DISSERTATION ON

CORRELATION AND IMPACT OF METABOLIC SYNDROME IN BIPOLAR DISORDER

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CERTIFICATE

This is to certify that this dissertation entitled "**CORRELATION AND IMPACT OF METABOLIC SYNDROME IN BIPOLAR DISORDER"** is the bonafide work of **Dr S.P.SABARITHA** in partial fulfilment of the requirements for M.D.(Psychiatry) BRANCH-XVIII Examination of The Tamilnadu Dr M.G.R. Medical University to be held in APRIL-2016. The period of study was from January-2015 to June-2015.

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DECLARATION

I, **Dr.S.P.SABARITHA**, solemnly declare that the Dissertation titled **"CORRELATION AND IMPACT OF METABOLIC SYNDROME IN BIPOLAR DISORDER"** is a bonafide work done by me in the Department of Psychiatry, Thanjavur Medical College and Hospital, during January-2015 to June-2015 under the guidance and supervision of **Dr.S.ILANGOVAN M.D.,** Professor & Head, Department of Psychiatry, Thanjavur Medical College, Thanjavur.

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INTRODUCTION

Bipolar Disorder is a chronic episodic illness with frequent alterations of mania and depression. Episodes of mania and depression are separated by periods of recovery and functional ability comparable to their pre-morbid levels. Jules Falret provided one of the earliest historical accounts of Bipolar Disorder and called it as "La Folie Circulare." Later the concept was further redefined when Emil Kraepelin segregated it from other psychotic illnesses leading to the separation of "Manic Depressive Psychosis" from "Dementia Praecox"

Course of Bipolar disorder vary from patient to patient, and it is not fully

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‘CORRELATION AND IMPACT OF METABOLIC SYNDROME IN BIPOLAR DISORDER’

Background:

Bipolar Disorder is a chronic episodic illness with frequent alterations of mania and depression. Various physical problems are known to affect the course and outcome of Bipolar Disorder. Out of them metabolic syndrome is a well-known co-morbid condition which shares common risk factors and also worsens the disease course, may contribute to premature mortality in Bipolar Disorder.

Hence, the knowledge about the metabolic abnormalities in Bipolar Disorder can help us in planning the treatment of Bipolar Disorder to get better prognosis. In this background the present study was conducted in patients with Bipolar Disorder to assess the relationship between them.

Aim:

To assess the impact and correlation of metabolic syndrome on Bipolar disorder patients.

Objective:

1. To assess the clinical correlates and socio demographic profile of patients with Bipolar disorder.
2. To assess the various metabolic parameters in Bipolar disorder patients.
3. To compare the clinical variables of Bipolar disorder in subjects with and without metabolic syndrome.

4. To evaluate the correlation between metabolic parameters and clinical variables of Bipolar disorder.

Methods:

A cross sectional study was conducted on patients of Bipolar Disorder attending Psychiatric outpatient department of Thanjavur Medical college, Thanjavur. Patients who fulfilled ICD-10 criteria for Bipolar Disorder were included in the study. All subjects underwent haematological evaluation to assess metabolic parameters like, blood glucose, lipid profile and also anthropometric parameters. Then they were divided into two groups, with and without metabolic syndrome. They were assessed by a semi-structured proforma for their socio-demographic status, life chart to assess their course of illness. Young Mania Rating Scale (YMRS; for mania) and Hamilton Depression Rating Scale (HAM-D; for depression) was administered to assess the severity of current episode.

Inclusion criteria:

1. All patients of Bipolar disorder (according to ICD-10) attending Psychiatric outpatient department of Thanjavur Medical College Hospital, Thanjavur.
2. Age 15 to 60 years.

Exclusion criteria:

1. Patients not willing to be a part of the study.
2. Patients with altered sensorium.
3. Pregnancy and post-partum (< 6 weeks after delivery or miscarriage).

Results:

The mean age of the study population was 39 years. More than half of them were males, majority of them being from rural areas, educated up to secondary level. Half the populations were employed, with women being mainly housewives. Majority were Hindus.

The criteria for the metabolic syndrome were satisfied by 49.18% of patients. The prevalence was seen to increase with age, and was higher in the male patients. The various components of metabolic syndrome were also found to be high. 64% patients were obese, 60.65% were having abdominal obesity, hypertension was present in 27.3%, low HDL found in 35.3%, increased triglyceride present in 29.5%, and increased fasting blood sugar was present in 24.59%. Patients of Bipolar disorder with metabolic syndrome were found to have a greater number of lifetime episodes, longer duration of illness, more frequent depressive episodes at onset and the life time depressive episodes were significantly higher in them.

Age of the patient, more number of lifetime depressive episodes and more total number of lifetime episodes were found to be associated with the development of metabolic syndrome.

Conclusion:

Increasing age, more number of lifetime depressive episodes and the more total number of lifetime episodes appear to be predictors for the

occurrence of metabolic syndrome in patients with Bipolar disorder. We thus have valuable insight about the relationship between metabolic syndrome and Bipolar disorder. The presence of metabolic syndrome influences the course and severity of the illness. It is possible to detect the presence of the metabolic syndrome and its components in the early stages of their development and plan timely intervention. This would help in altering the course and severity of the illness in a favorable manner.

Key words:

Bipolar Disorder, Metabolic syndrome, Body Mass Index, Waist circumference, Dyslipidemia

INTRODUCTION

Bipolar Disorder is a chronic episodic illness with frequent alterations of mania and depression. Episodes of mania and depression are separated by periods of recovery and functional ability comparable to their pre-morbid levels. Jules Falret provided one of the earliest historical accounts of Bipolar Disorder and called it as "La Folie Circulare." Later the concept was further redefined when Emil Kraepelin segregated it from other psychotic illnesses leading to the separation of "Manic Depressive Psychosis" from "Dementia Praecox"

Course of Bipolar disorder vary from patient to patient, and it is not fully benign, with recent studies suggesting that Bipolar Disorder patients experience significant degree of chronicity than previously thought. Various physical problems are known to affect the course and also the outcome of Bipolar Disorder. Epidemiological studies indicate increased mortality rate in Bipolar disorder patients as compared to the general population. One of the major factors conditioning to this is the occurrence of obesity, hypertension, dyslipidemia, abnormal glucose levels among these patients. Metabolic syndrome, is a combination of metabolic abnormalities, is a well-known co-morbid condition which tends to share common risk factors with Bipolar disorder and also worsens the disease course, may contribute to premature mortality. It is now identified as the risk factor for cardiovascular disease and Type 2 Diabetes mellitus. These findings emphasize the

need for identification and early intervention of metabolic abnormalities which can modulate the severity of the illness to a great extent and reduce the morbidity & mortality associated with the illness.

Most of the present data on Bipolar disorder patients with comorbid metabolic syndrome emanates from western studies. India is reported to have higher rate of early onset diabetes and hypertension. With this background there is a need to explore the relationship between metabolic abnormalities and Bipolar disorder in Indian context. The present study is one such attempt.

AIM & OBJECTIVE

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HYPOTHESIS

The clinical and socio demographic profile of Bipolar disorder patients with metabolic syndrome is different from those without metabolic syndrome.

REVIEW OF LITERATURE

PREVALENCE OF METABOLIC ABNORMALITIES:

The burden due to Bipolar disorder (BPD) is mainly related to psychiatric symptoms and dysfunction related to the disease; other medical co-morbidities are also common in this Bipolar disorder (1). There is a higher prevalence of metabolic abnormalities in BPD patients when comparing to the general population (2, 3 and 4). BPD patients found to have a wide array of metabolic abnormalities like weight gain, hypertension, dyslipidemia, diabetes mellitus and abnormal thyroid functions which has impact in its course and outcome in an adverse manner (5, 6).

OBESITY IN BIPOLAR DISORDER

The prevalence of obesity was found to be consistently high in association with Bipolar disorder (6, 7 and 8). The objective measurement of obesity being done by measuring waist: hip ratio and body mass index (BMI). BMI is a quantitative measurement of obesity (estimated by body weight in kilogram / height in meters square). While the waist: hip ratio is the assessment of the type of body fat distribution. Based on the BMI, WHO classified obesity (9) as BMI greater than 30 and BMI more than 40 considered as morbid obesity.

It is important to note that of late WHO has modified obesity criteria for Asians (10), obesity could be defined as BMI above 25 and over weight when BMI is more than 23. Central obesity is defined as waist circumference >80cm

for women and waist circumference >90cm in men by the same WHO criteria (10). This was probably in light of a study done by WHO which found that urban Asians with a BMI between 23-24 have an equivalent risk of hypertension, diabetes mellitus, and dyslipidemia as a BMI in the range of 25-29.9 in white population (10 and 11).

Individuals with Bipolar disorder are at a risk for obesity due to multiple factors like sedentary life style, eating habits and medications (5). Over-weight, obesity and extreme obesity are common in people with Bipolar disorder (12). Elmslie et al (7) studied eighty nine euthymic Bipolar outpatients with sex matched control subjects and found that female subjects were more often obese (20% vs 13%) and overweight (44% vs 25%) when comparing to their female controls. Male subjects were more often found to be obese (19% vs 10%) than their male controls. Distribution of the excess fat in the Bipolar patients was more at central, with fifty nine percent of female patients compared to seventeen percent of female controls; they had waist: hip ratio >0.8 (statistically significant) and 58% of male patient compared to 35 % of male controls having waist: hip ratio >0.9 (statistically significant)[7].

Pharmacotherapy showed impact on body weight; study on 50 patients showed increase in body weight in 32% of patients on comparing with only 19.8% in controls (13). A Danish study (14) reported that weight gain was associated with female gender, weight at diagnosis, and antidepressant use but

not with thyroid concentration or lithium or antipsychotic use. Likewise another study found that weight gain was associated with antipsychotic use but not with lithium use (7).

Most important factor related to increase in obesity related diseases is weight gain and another factor is excessive centrally deposited adipose tissue. Prediction of coronary heart disease is significantly associated with distribution of body fat rather than total body fat (15 and 16).

HYPERTENSION IN BIPOLAR DISORDER:

There are reports stating that Bipolar disorder patients are found to have high blood pressure; they also have elevated risk for death due to cardiovascular diseases (17-19). The systolic blood pressure was higher during manic episode when compared to the baseline (17). The underling pathophysiological process for the high blood pressure is proposed to be the abnormal regulation of the sympathetic nervous system. One of the recent studies found out an interesting finding that the resting heart rate did not differ in euthymic Bipolar patients. However, people with Bipolar disorder did have significant lower heart rate variability (20). Excessive regularity in heart rate may reflect a level of cortisol control that has been reset to withstand stressful changes in relation to mood stability. This may dampen changes associated with fluctuation of mood and also may contributes to cardiac fluctuations (20). There are some studies which studied uptake of glucose by the central nervous system which is done by

insulin in response to the oral intake of glucose; they found that there is significant overlap between this mechanism and the sympathetic overactivity; they suspect this mechanism to be an etiopathogenesis of hypertension in BPD patients (21). Sympathetic activity was also found to be high in obesity (22). Some studies link increased hypothalamo-pituitary axis activation to the increased sympathetic activity; they also say that, this has better correlation than the insulin related mechanism (23); so they suggest both hypothalamo-pituitary axis activation and sympathetic over activity go hand-in-hand.

DYSLIPIDEMIA IN BIPOLAR DISORDER

Dyslipidemia is common among patients with Bipolar disorder. About two-third of Bipolar patients were found to have borderline dyslipidemia and a quarter met the criteria of high risk dyslipidemia. Grover et al (24); in this review of 19 studies reported prevalence of abnormal serum level of HDL ranging from 21.7 – 71 and triglyceride level from 22.7 -58.8 among patients of Bipolar disorder. Lipid profile of Bipolar disorder patients is influenced by many other confounding factors like overweight, diabetes mellitus and medications (25). Serum lipid level probably has a clinical correlation, manifested as violence and suicidal behaviour in Bipolar patients (25). Simon J. Evan et al (26) reported a positive correlation between personality factors and violent reaction with low plasma lipid levels in the patients of Bipolar disorder. Engelberg (27) proposed as the cholesterol is an important ingredient of the

neuronal cell membrane, which plays an important role in the transport of neurotransmitters hence modulating its effects. Lower cholesterol levels found to be associated with central serotonergic dysfunction and results in aggressive and impulsive behaviour (28).

DIABETES MELLITUS IN BIPOLAR DISORDER

High rates of insulin resistance and impaired glucose tolerance in individuals with psychiatric illnesses were recognized even before the introduction of neuroleptics (29 and 30). Comparing with general population BPD patients were more commonly found to have impaired glucose tolerance and insulin resistance is found to be more common in individuals with Bipolar disorder than in the general population (31). Studies have established depression as an independent risk factor for diabetes (32) and this link has been explored in Bipolar patients as well. When comparing with general population Bipolar patients who were hospitalized have significantly high prevalence (three fold high; i.e. 9.9% Vs 3.4%) of diabetes mellitus (33; Cassidy et al). Diabetes mellitus is more prevalent in schizophrenia and so schizophrenia is taken as an independent risk factor for diabetes mellitus; some studies revealed that it is also equally prevalent in Bipolar patients as in schizophrenia (34) while other studies have found the rates of diabetes mellitus was actually higher in Bipolar patients (26% Vs 13% ; $p<0.006$) (35).

Theories link a tyrosine hydroxylase / insulin / insulin-like growth factor II(TH/INS/IGF-II) gene cluster on the short arm of chromosome 11 as a susceptibility locus for diabetes mellitus (36, 37) and link tyrosine hydroxylase marker to an association with Bipolar disorder (38, 39). Patients with Bipolar disorder with diabetes mellitus are reported to experience more severe and chronic course, with greater numbers of episodes, with significantly more rapid cycles (40) and longer duration of hospitalization than non-diabetic patients (33).

THYROID ABNORMALITIES IN BIPOLAR DISORDER:

Thyroid hormone is related to wide variety of bodily functions. Hence thyroid dysfunction leads to variations in various metabolic parameters. Thyroid abnormality may present as hyperthyroidism and hypothyroidism and the later may be subclinical or overt. Thyroid abnormalities are studied in Bipolar patients. Hypothyroidism in BPD patients is linked to more likelihood of depressive episodes; hyperthyroidism leads to more manic or euphoric episodes (41). These thyroid abnormalities are also leads to increased cardiovascular related mortality and morbidity (42-45).

Thyroid dysfunction in BPD patients has significant role in its prognosis. These patients show poor response to pharmacotherapy than those with normal thyroid function (46).

Thyroid abnormality in BPD patients is also linked to Lithium therapy (47). Lithium is known to inhibit the release of thyroid hormone and so results in hypothyroidism with elevated TSH levels. There are studies available on role of thyroid supplement to patients on lithium (47).

FORMULATION OF METABOLIC SYNDROME:

The metabolic syndrome is a mixture of parameters which makes the patients more vulnerable to cardiovascular and diabetes related morbidity and mortality. The basic pathology is central obesity and insensitivity to insulin. There are some other pathologic factors for this syndrome; they include physical inactivity, non-alcoholic steato-hepatitis, polycystic ovarian disease and hereditary lipodystrophies.

There are few diagnostic criteria available for this syndrome. One of them is WHO criteria. It states that:

1. Abnormal waist-hip ratio.
2. Decreased HDL level.
3. Elevated triglyceride level.
4. High fasting glucose level.
5. Hypertension.

If three of the five had been there, then the patient is said to have metabolic syndrome according to WHO criteria.

Another one, the Third Report of the US National Cholesterol Education

Program, Expert Panel on Detection, Education, and Treatment of High Blood Cholesterol in adult is the most often cited definition. Most criteria require three parameters to be abnormal to be called as metabolic syndrome.

Another criterion called International Diabetes Federation (IDF) and National Cholesterol Education Program Adult Treatment Panel-III is available. According to IDF waist circumference abnormality is an essential criterion; and needs other two criteria to be called as metabolic syndrome.

There are steps being taken to make the criteria uniform.

ASSOCIATION BETWEEN METABOLIC SYNDROME AND BIPOLAR DISORDER:

There is overlap between symptoms of Bipolar disorder and metabolic syndrome (57). Comparing with the general population prevalence of metabolic syndrome is significantly plenty in Bipolar disorder patients. The prevalence was even higher in hospitalized Bipolar patients as compared to the community sample (56% Vs 25%). A meta-analysis of 37 studies (58) reported that the prevalence of metabolic syndrome was around 37.1 % in the Bipolar disorder patient. Further Grover et al (24) reported that the prevalence of metabolic syndrome range from 16.7 to 67 in his review of 34 studies. In the same review Grover et al (24) pointed that waist circumference (WC) and raised blood pressure (BP) were the most common abnormal parameters reported across 19 studies. Raised waist circumference was seen in 30-85% of Bipolar patients,

while 6-62% were found to have a raised blood pressure or were already on antihypertensive medication. Elevated fasting blood glucose or patients on oral hypoglycemic medication were the least commonly reported (6-43.5%), Low level of high density lipoprotein (HDL) were seen in 21.7-67.6%, and high triglyceride level in 22.7-58.8%. Lipid abnormalities were of intermediate prevalence (24). Fagiolini et al (6) enumerated these metabolic abnormalities in a group of 171 patients of Bipolar disorder and reported 74% of these patients were obese particularly the abdominal type of obesity was most common (49%) in addition to that 41% were hyperglycemic , 48% were with elevated triglycerides or were receiving cholesterol- lowering medication, 23% were having low levels of HDL cholesterol, 39% were hypertensive and 8% had high fasting glucose or were on anti-diabetic medication use (6).

Differing findings in these studies may be due to difference in sample size and also the different diagnostic criteria used for Bipolar disorder and metabolic syndrome; variation in sample composition method and the difference in method of taking anthropometrics and metabolic parameters (58). Striking geographical variation also noted in the prevalence of metabolic syndrome in patients with Bipolar disorder (58). Prevalence of metabolic syndrome was highest in New Zealand and Australia (64.2%) followed by South America (38.2%) and Europe (32.4%), further prevalence was higher in North America (49.3%), prevalence in Asian countries was 39.6%.

DETERMINANTS OF METABOLIC SYNDROME:

Metabolic syndrome and Bipolar disorder have overlapping physical factors like obesity. They also share abnormalities in metabolism of glucose and insulin, and hormonal and neuronal abnormalities like the hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-thyroid (HPT) axis (34).

Along with these overlapping physical factors, drugs used for the treatment of Bipolar disorder also increases the symptoms of Bipolar disorder; they are known to cause increase in weight, metabolic abnormalities, disturbances in lipid and glucose metabolism, which predispose to diabetes mellitus, and other metabolic abnormalities (59).

Factors predispose to the metabolic syndrome in the patients of Bipolar disorder can be summarized under following main headings:-

1. Genetic
2. Endocrine
3. Lifestyle and behavioural risk factors
4. Pharmacotherapy induced metabolic syndrome

1. GENETIC FACTORS:-

Advancement in medical technology identified the association of genetics of Bipolar disorder and the metabolic syndrome. They found that seven different diseases (including Bipolar disorder) have a common biological pathway (60).

Further analysis of this sharing of genetic basis leads to identification of strong correlation of genetics between the following three conditions (60).

- Bipolar disorder.
- Coronary artery disease.
- Type-2 diabetes mellitus.

2. ENDOCRINE:-

Correlation of Bipolar disorder and metabolic syndrome could be attributed to sharing of common systems like HPA axis (41), the immune system (61 and 62), autonomic nervous system, glucose and insulin regulation, and regulation of homeostasis (63). There are studies highlighting the higher prevalence of hypothalamo-pituitary axis abnormalities of in Bipolar disorder patients than in general population (41). Presence of stress, both in manic and depressive episodes, elevates the serum cortisol (64). Evidence also suggests that psychological stressors may predate the onset of Bipolar disorder (65 and 66) and also the relapse (67). The most important neuroendocrine pathology in major depression is overactivity of the hypothalamic-pituitary-adrenal (HPA) axis which is considered the central control of the stress response (68).

Various neuroendocrine abnormalities had been demonstrated in Bipolar disorder patients. Few of them are the followings:

1. Disturbances in normal diurnal variation in cortisol level.
2. Increased basal cortisol level.

3. Loss of normal suppression of cortisol level by dexamethasone.

4. Disturbed response of HPA axis to various stressors.

Abnormalities in cortisol are not confined to the depressive phase, with abnormal dexamethasone/corticotrophin-releasing hormone (DEX/CRH) test results being found in people with mania as well (74). Medication used in either phase may have an impact on the cortisol response. The abnormalities of HPA axis may be normalized in following treatment of depressive symptoms (75, 76); but one study showed different result with no such normalization (77).

Regarding treatment of resistant unipolar depression Lithium augmentation increased the cortisol response to dexamethasone suppression test (78); although another recent study of people with Bipolar disorder did not show this increase (72). A treatment study of people with schizophrenia found that typical neuroleptic drugs suppress blood cortisol levels and decreased the number of patients who are dexamethasone non suppressors (79).

HYPOTHALAMIC-PITUITARY-ADRENAL AXIS:-

Various derangements in hypothalamic-pituitary-adrenal axis are seen, this leads to persistent elevation of the cortisol. Elevated cortisol makes the following cascades.

- Blunts the insulin mediated uptake of glucose by the cells; it leads to elevated blood glucose level; the elevated glucose is converted

into fat and gets deposited in coronary arteries to produce coronary artery disease.

- Impaired leptin signalling: this brings the obesity.
- Persistently elevated cortisol also promotes deposition of fat in viscera.
- Action on lipoprotein lipase: Promotes influx of fat into adipose tissues. As more fat is deposited in the viscera, triglycerides are getting attracted more and get accumulated.
- Promotion of insulin resistance.

IMMUNE FUNCTION:-

There are known linkage between the Bipolar disorder and the immune pathways. Both mood disorders produce abnormality in immunity and immune derangements produce mood disorders. Later was demonstrated in few studies and they showed various mood disturbances like, altered sleep, anorexia and anhedonia can be produced by administration of various inflammatory mediators. These exposures to inflammatory mediators are known to cause depression (88 and 89).

Conversely immune response is also altered in mood disorders. Overexpression of various immune mediators had been demonstrated in mood disorders, especially in depression (61 and 62). These studies suggested the

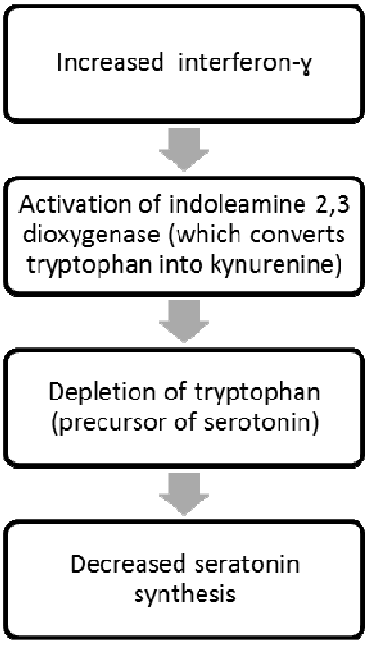
linkage between the mood disorders and overexpression of pathways of immune process. More than this they also demonstrated that this overexpression comes to normal after psychotherapy for the depression (87).

Several immune mediators have been linked to Bipolar disorder. Out of this interleukin-6, C-reactive protein and interferon- γ are playing the major role. Level of these mediators also shows correlation with cardiac related morbidity and mortality.

Interleukin-6: Interleukin-6 level is increased in depression; this is mediated by leptin. This results in increased adipocyte deposition and thereby obesity. It results in increased obesity related morbidity and mortality. Another important effect of elevated interleukin-6 is its effect on corticotrophin releasing hormone. Interleukin-6 is a strong stimulator for production of corticotrophin releasing hormone. It leads to increased hypothalamo-pituitary axis activation and thereby results in increased cortisol level in blood (95). This blunts the cellular and humeral immune response. So the final picture is elevated immune mediators but with blunted immune response (96).

C-reactive protein: C-reactive protein is also elevated in depression. It is secreted by liver. It shows strong correlation with cardiac related morbidity and mortality.

Interferon-γ: This is shown to be related to Bipolar disorder recently. It causes cascade of events as below (97).



Another effect of the above cascade is effects of 3-hydroxy- kynurenine and quinoline, which are metabolites of the above sequence causing damage to brain parenchyma (97 and 98).

More than these elevated inflammatory mediators are also linked to the following diseases:

1. Osteoporosis.
2. Cancer.
3. Inflammatory arthritis.
4. Alzheimer's disease.

3. LIFE STYLE AND BEHAVIOUR:

Behavioural patterns and life style are also known to have significant role in the co-incidence of the metabolic syndrome and Bipolar disorder. Lack of exercise (57, 102-104), poor eating habit (105), and especially substance use

are the important contributors (106).

Substance abuse disorders had been demonstrated to have higher incidence in Bipolar disorder patients than in general population. In general population the incidence was 12.8%; but in Bipolar disorder it is shown to be significantly higher at 35.3% (108) (NESARC; study on 43093 respondents). They also demonstrated the 12-month prevalence of substance use disorders, which was about 27.9% in mania patients and 26.6% in hypomania; but the same was only 9.4% in the general population (108).

In another study (109) on Bipolar disorder patients nicotine dependency was significantly higher at 70%; and use / abuse of alcohol was also greater than the general population. In another study the alcohol use in Bipolar disorder patients was reported to be 21.4 to 54.5% (110).

Other life style factors associated with development of obesity and metabolic syndrome in Bipolar disorder patients are lack of physical activity and overeating (57, 102-104).

There are multiple known factors which cause obesity and metabolic abnormality. They can be listed as following:

1. Increased calorie intake.
2. High refined sugar intake.
3. Increased proportion of energy intake from carbohydrate.
4. Higher intake of sugar containing drinks.

All these factors are found to be high in case of patients of Bipolar disorder on a study by Elmslie et al (105).

Apart from all these factors basal metabolic rate is also found to be low in Bipolar disorder patients than normal controls (111) (Soreca et al).

Pattern of eating is also found to be abnormal in Bipolar disorder patients. They are controlled by dopamine mediated reward- like systems and their abnormality shows significant association with Bipolar disorder (112, 113 and 114).

In patients with decreased dopamine level in these reward pathways, it has been called as 'reward deficiency syndrome'. In this setting there are many compensatory mechanisms which cause increased intake of food by reinforcing behaviours (114, 115).

There are strong evidences for strong association, in female patients of seasonal affective disorder, between a gene variant called, the 7-repeat allele of the dopamine-4 receptors gene, which decreases affinity for dopamine, and binge-eating behaviour (116).

Binge eating is also a common associated morbidity in Bipolar disorder patients. In a study by Ramacciotti et al (117), they demonstrated that 27.5% of patients with Bipolar disorder encountered diagnosis of binge eating disorder / bulimia nervosa, either as a current diagnosis or in their life time. Kruger et al also showed similar results (118).

Health care seeking behaviour also is deranged in Bipolar disorder patients when comparing with normal population. So many of the illnesses in these patients are underdiagnosed or go unnoticed in these patients (119). Cradock-O'Leary et al (120) also founded similar results in Veterans Affairs (VA).

4. PHARMACOTHERAPY:-

Both typical and atypical antipsychotics are available in treatment of Bipolar disorder. Because of extra-pyramidal side effects typical antipsychotics had been widely replaced by the second-generation antipsychotics (121, 122).

There are studies available stating that metabolic syndrome related adverse effects are more common with atypical antipsychotics when comparing with mood stabilizers (6, 123 and 124). Various other adverse effects related to metabolic syndrome had been demonstrated with second generation antipsychotics. They show more weight gain and abnormalities in carbohydrate and fat metabolism (125). Out of atypical antipsychotics clozapine and olanzapine are known to have higher incidence of metabolic syndrome related adverse effects and weight gain; they show higher incidence of diabetes mellitus and hyperlipidaemia (121); risperidone and quetiapine show little lesser incidence of these effects than the previously mentioned drugs (121).

Mechanism of action for the adverse effect of these drugs had been studied. Histamine receptor mediated action of clozapine caused over activity of the adenosine phosphate – protein kinase. This enzyme is related to appetite,

overexpression of which causes increased appetite and over intake of food (126).

On the other case metabolic syndrome related adverse effects are not significantly encountered or not at all in aripiprazole and ziprasidone (121), but needs further studies.

Mood stabilizers are also shown to produce weight gain. Several studies demonstrated the occurrence of weight gain with these drugs. Monotherapy with lithium showed 13% incidence of significant weight gain after one year; this was around 21% for Divalproex; comparing with placebo it was seen only in seven percent of subjects (127) (Bowden et al).

Lithium was shown to have effect on carbohydrate metabolism. Action of lithium on carbohydrate was similar to insulin, with augmentation of glucose absorption in gastrointestinal tract and increases appetite (128, 129). On the other hand valproate influences fat metabolism (130).

Thirst is also increased by these drugs (131); this may result in high intake of sugar containing high calorie drinks which results in weight gain. Furthermore appetite is also increased by these drinks. Action on hypothalamus is said to be the cause of increase in thirst.

Other mood stabilizing drugs did not show significant weight gain. Monotherapy with lamotrigine for Bipolar disorder did not showed significant weight gain in study by Sachs et al (132). Similar to their study

Ketter et al did with carbamazepine; they also reported no weight gain after six months (133).

Regarding antidepressants mechanism of action for adverse effects differs for each class of antidepressants. Tricyclic antidepressants, which are adrenergic, so they blunt response to insulin and causes hyperglycaemia. Whereas drugs acting via serotonin, i.e. SSRI have different action; they show favourable actions on carbohydrate metabolism, causing glycaemia control (134). So that weight gain is more common with tricyclic antidepressants than SSRIs. Mirtazapine is an exception, as the mechanism of action is between tricyclic agents and SSRI, they show higher incidence of weight gain than others (135).

IMPACT OF METABOLIC SYNDROME ON BIPOLAR DISORDER

Bipolar disorder is one of the leading causes of worldwide morbidity and premature mortality, according to WHO it is in the top ten (136). It also has been suggested that it causes more economic burden than other behavioural health conditions (137). It causes more illness burden and more need and use of health services which directly increases economic burden. It also causes interferences in work flow function (137 and 138).

It not only shows its own individual risks, but it also adds additional co-morbid conditions which adds risks further (139); it is seen that there is six fold increase in diabetes mellitus (140). Whereas risk for coronary artery disease

related mortality is increased by three to six times (139, 141 and 142).

Most common cause of mortality in Bipolar disorder patients is cardiovascular disease related death. Another cause of death in these patients was endocrine related complications. There was three times increase in this complication in these patients comparing with general population (19).

There are other diseases associated with Bipolar disorder, as listed earlier they include, fatty infiltration of liver, polycystic ovarian disease, gall stones & lipid derangements. Apart from all these diseases they also show increased tendency to commit suicide. As a whole the life expectancy has been reduced (138).

Grover et al (24) in his review of 34 studies pointed some clinical correlates of metabolic syndrome Bipolar disorder patients. These are longer duration of illness,[144,145] greater numbers of life time depressive and manic episodes with more intense and treatment resistant index affective episodes (146), depressive onset (147); index manic episodes were less severe (148); age of onset at index episode was delayed; first treatment for both phases are delayed (149). The use of different criteria of metabolic syndrome and the effect of ethnic and geographical factors play a significant role in the pattern and prevalence of metabolic syndrome.

In this aspect most of the information is contributed by western studies and Indian data is sparse. Moreover the studies do not investigate the relationship between types of index episode, total number of lifetime episodes, and severity of the current illness with the prevalence on metabolic syndrome. The present study attempts to explore these associations. On the back ground of high prevalence of early onset diabetes and hypertension in the Indian population there is a need for examination of the relationship between metabolic syndrome and Bipolar disorder and hence the requirement for the present study.

MATERIALS AND METHODS:

Study setting:

The present study was conducted on patients attending Psychiatric outpatient department of Thanjavur medical college hospital, Thanjavur, Tamil Nadu.

Study period:

From January 2015 to June 2015.

Study design:

A Cross sectional study.

Sample size:

61 Patients who fulfilled ICD-10 criteria for Bipolar disorder have been included in the study.

Inclusion criteria:

1. All patients of Bipolar disorder (according to ICD-10) attending Psychiatric outpatient department of Thanjavur Medical College Hospital, Thanjavur.
2. Age 15 to 60 years.

Exclusion criteria:

1. Patients not willing to be a part of the study.
2. Patients with altered sensorium.
3. Pregnancy and post-partum (< 6 weeks after delivery or miscarriage).

METHODS OF DATA COLLECTION

The study protocol was presented to the Ethical Review committee of Thanjavur Medical College and got approved. The study was conducted at the Department of Psychiatry of Thanjavur Medical College in Thanjavur. Male and female patients with age more than 15 years with diagnosis of Bipolar disorder (according to ICD-10), were included in the study. Prior to recruitment into the study a written informed consent was obtained from all the patients.

- Socio-demographic characteristics and clinical details of all the subjects were recorded using a semi-structured pro forma.
- Sample was selected by purposive sampling and allocated to the inclusion or exclusion group.
- 61 patients with a diagnosis of Bipolar disorder were assessed over a 6 months period (From January 2015 to June 2015).
- Psychiatric diagnosis was made by using the criteria according to International Classification of Diseases - Tenth version (ICD-10).

ASSESSMENT:

- A detailed assessment of anthropometric parameters like height (cm), body weight (kg) and body mass index (BMI), waist circumference (cm) was made.

- Fasting venous blood sample was collected with aseptic precautions and sent to laboratory for the examination for blood glucose, serum lipid, and thyroid profile.
- The severity of symptoms of present depressive episode was assessed by using Hamilton Depression Rating Scale (HDRS).
- The severity of symptoms of present manic episode was assessed by using Young Mania Rating Scale (YMRS).
- Metabolic syndrome was ascertained by using a consensus definition[56] according to which three or more criteria are required to be satisfied. The criteria are high blood pressure (≥130/85), high triglycerides level (>150 mg/dl), low level of HDL (<40 mg/dl for male and <50 mg/dl for female), impaired fasting sugar (≥100 mg/dl), and high waist circumference (>90 cm for males and >80 cm for females).

PHYSICAL EXAMINATION AND **ANTHROPOMETRIC MEASUREMENTS:**

General physical examination was done including pulse and blood pressure measurement according to the prescribed methods

EXAMINATION OF PULSE

Pulse is peripheral extension of the heartbeat. To measure the pulse at the wrist of participants, examiner's index and middle fingers of right hand were used to locate the pulse on the wrist at the base of the thumb. Using a watch with a second hand, pulse was counted for 1 minute to get the pulse rate.

MEASUREMENT OF BLOOD PRESSURE:

Blood pressure is measured using standard mercury manometers in supine position. The cuff was wrapped around upper arm at about the level of heart and inflated till the pressure sufficient to obliterate the vessel; then the cuff was deflated slowly. A stethoscope was placed over brachial artery region to listen for Korotkoff sound. With gradual deflation of the cuff, the point of appearance of clear tapping sound in time with the heart beats was taken as the systolic blood pressure. As the cuff deflated further, the sound would become quieter; before disappearance it gets louder. The point at which the sound disappeared was taken as the diastolic blood pressure. In cases of elevated pressure above ≥130/85, two readings were taken at 5-minute intervals; a third measurement also may be taken in the setting of only one measurement is elevated in the initial two measurements. The third reading was taken after 30 minutes; the lowest of these reading was included for analysis.

MEASUREMENT OF BODY WEIGHT:

To measure the weight, individual was first asked to remove their shoes, and heavy garments, and empty their pockets of heavy articles that could affect the correct recording of weight. Next, they were asked to stand on a weighing scale placed on a hard-floor with reading set at zero with weight distributed evenly to both feet. He/she was then, asked to look straight and the weight was recorded on the scale in kilograms.

MEASUREMENT OF HEIGHT:

To measure the height, individuals were asked to remove their shoes. Then he/she was asked to stand with his/her back to the height rule. The back of the head, back, buttocks, calves and heel would be touching the wall with feet placed together. They were then asked to look straight so that the top of the external auditory meatus (ear canal) was at level with the inferior margin of the bony orbit. The head piece of the stadiometer or the sliding part of the measuring rod was lowered so that the hair (if present) is pressed flat. The height was then recorded to the nearest centimetre unit shown on the scale.

MEASUREMENT OF WAIST CIRCUMFERENCE:

To measure the waist circumference of the subjects, individual was asked to remove tight clothing, including the belt and be without heavy outer garments. He/she was made to stand with their feet fairly close together and their weight equally distributed to each leg. Participants were asked to breathe normally; the reading of the measurement was taken at the end of gentle exhalation. Waist circumference was measured at a level midway between the inferior costal margin and superior iliac crest, at the end of normal expiration while standing, with the help of a tape all around the body in horizontal position, measurement recorded at the point of resolution of the tape.

CALCULATIONS OF BODY MASS INDEX (BMI):

The body mass index (BMI) or "Quetelet index" is a measurement of human body fat; it is based on two parameters; one is individual's weight and another is vertical height.

Body mass index (BMI) is calculated by dividing the subject's body weight in kilograms by the height in meter square.

Formula: - BMI = weight (Kg) / Height $(m)^2$.

BLOOD INVESTIGATION & METABOLIC PARAMETERS:

Under aseptic precaution fasting venous blood sample was collected; estimation of fasting blood sugar (FBS), post prandial blood sugar (PPBS), thyroid profile, and lipid profile were done.

DESCRIPTION OF TOOLS USED

SEMI-STRUCTURED PROFORMA

A semi structured proforma was applied to document socio-demographic and clinical details. For the documentation of course of the Bipolar disorder in the patient life chart method was used and the severity of the episode was assessed by using appropriate scales.

HAMILTON DEPRESSION RATING SCALE-21 (HDRS) [150-152]

Rating scale for depression developed by M Hamilton is called as the HDRD (also known as Ham-D); it is the most commonly scale for depression assessment. Seventeen items are there in the original version. It has been proved that it is not only useful in the initial assessment, but also in the treatment follow up. Clinician interviews the patients and asks for particular symptoms; e.g., depressed mood, guilty feelings, suicide thought, and disturbance in sleep, level of anxiety and loss of weight. It takes around fifteen minutes to complete the interview and scoring. The clinician puts score for each symptom which is constructed that ranges from 0 (not present) to 4 (extreme symptoms).

YOUNG MANIA RATING SCALE (YMRS) [153, 154]

The Young Mania Rating Scale (YMRS) is also a most commonly used rating scales, but for assessment of manic symptoms. It has been designed with eleven items; it is a subjective report based on based on the patients, fregarding their clinical condition over the previous 48 hours. Other informations are taken during the interview based on clinical observations. Published descriptions are available for selecting items.

It follows the Hamilton Rating Scale for Depression (HAM-D) style, with each item given a severity rating. Irritability, speech, thought content, and

disruptive/aggressive behaviour are the four items that are graded on a 0 to 8 scale; rest seven items are graded on a 0 to 4 scale. Weightage for individual items also differs; these above mentioned four items are given two fold weights of the others; the basis is to compensate poor cooperation in severely ill patients. Different anchor points are available for each severity grade.

There are lot of variations in the baseline sore of YMRS. It mainly depends on the clinical presentation of the patients, like in depression (YMRS = 3), euthymic (YMRS = 2) & in mania (YMRS = 12). Sometimes a clinical study entry requirement of YMRS > 20 generates a mean YMRS baseline of about 30. The advantage of YMRS includes, it is widely accepted, easy to administer and its brevity and its limitation includes, it is mainly used in patients with the diagnosis of mania. YMRS is mainly used in the evaluation of symptoms of mania at the baseline and also during disease progression. The time required for the administration of YMRS is usually 15-30 minutes and is routinely done by psychiatrists or any experts who trained in administering it.

STATISTICAL METHODS

The Statistical Package for Social Science (SPSS) version 16.0 was used for statistical analysis. For continuous variables Mean and standard deviation were calculated. For nominal and ordinal variables Frequencies with percentage were calculated. Chi-square and t- test/ANOVA were used for comparisons as applicable.

To assess the effect of independent variables on presence of metabolic syndrome, a binary logistic regression was performed. Pearson's correlation test was employed to examine the relationship between illness parameters. A $p=<0.05$ was considered to be statistically significant.

Table - 1 : Mean age of the sample:

Age	**Mean**	**S.D**	**t**	**Df**	**Statistical inference**
With Metabolic Syndrome (n=30)	46.77	6.067	6.588	59	0.000<0.05 **Significant**
Without Metabolic Syndrome (n=31)	33.29	9.480			

Study population was divided into two groups. Mean age of the Bipolar disorder patients with metabolic syndrome was found to be 46.77 ± 6.067 years. Mean age of Bipolar disorder patients without metabolic syndrome was found to be 33.29 ± 9.480.

The difference between the two groups was statistically significant.

Table - 2: Age distribution of the sample.

Age	With metabolic syndrome (n=30)	Without metabolic syndrome (n=31)	Total (n = 61)
15-30 YEARS	2 (6.67%)	11 (35.48%)	13 (21.31%)
31-45 YEARS	12 (40%)	17 (54.84%)	29 (47.54%)
46-60 YEARS	16 (53.33%)	3 (9.68%)	19(31.15%)

This table shows the age wise distribution of the sample. Mean age of the sample population was found to be 39.92 years. Most of the Bipolar disorder patients with metabolic syndrome fell in the age group between 46-60 years (53.33%) and Bipolar disorder patients without metabolic syndrome are in the age group between 31-45 years (54.84%).

FIGURE 1: AGE DISTRIBUTION.

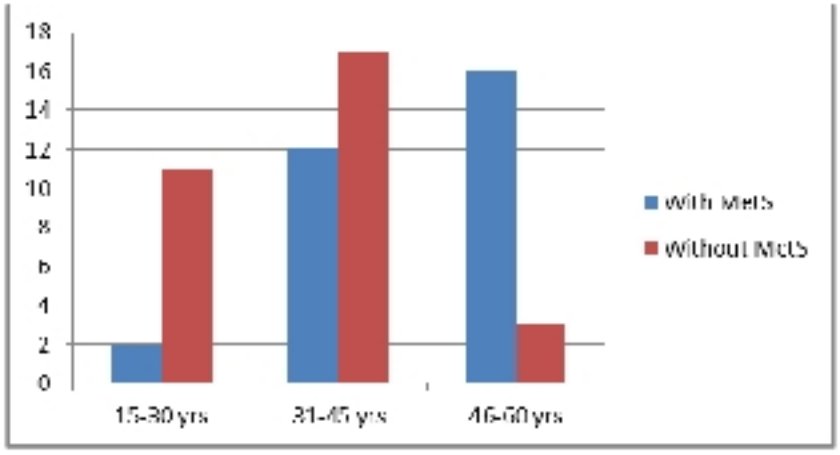


Table - 3: Sex distribution of the sample.

Sex	**With metabolic syndrome (n=30)**	**Without metabolic syndrome (n=31)**	**Total (n=61)**	**Statistical inference**
Male	16 (53.3%)	16 (51.6%)	32 (52.5%)	X^2=.018 Df=1 .893>0.05 Not Significant
Female	14 (46.7%)	15 (48.4%)	29 (47.5%)	

This table illustrates the sex distribution of the sample. 47.5% of the total sample population were Females and 52.5% were males. There is no significant difference between two groups.

FIGURE-2: SEX DISTRIBUTION.

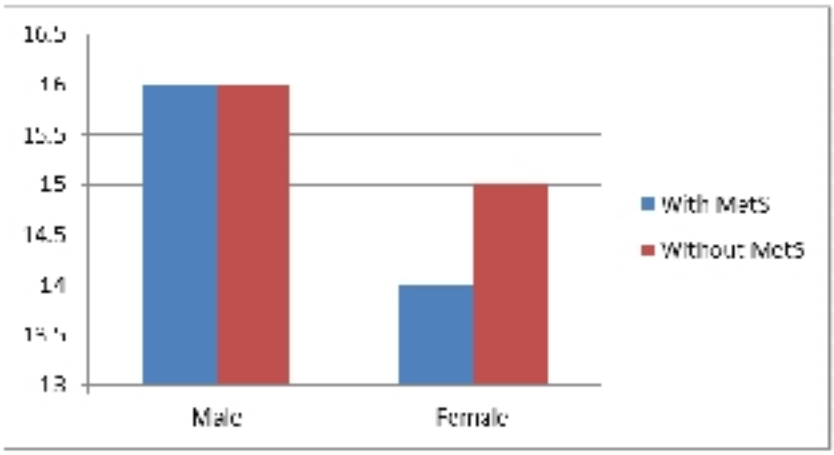


Table - 4: Religion distribution of the sample:

Religion	**With metabolic syndrome (n=30)**	**Without metabolic syndrome (n=31)**	**Total (n=61)**	**Statistical inference**
Hindu	26 (86.7%)	28 (90.3%)	54 (88.5%)	X^2=.201 Df=1 .654>0.05 Not Significant
Non Hindu	4 (13.3%)	3 (9.7%)	7 (11.5%)	

The above table shows the distribution of religion in the study population. It was found that around 88.5% of the total sample population were Hindus and 11.5% were Non Hindus.

The difference between the two groups with respect to religion was statistically not significant.

Table - 5: Educational status of the sample.

Education	With metabolic syndrome (n=30)	Without metabolic syndrome (n=31)	Total (n=61)	Statistical inference
Primary	11 (36.7%)	17 (54.8%)	28 (45.9%)	X^2=2.027 Df=1 .154>0.05 Not Significant
Secondary & above	19 (63.3%)	14 (45.2%)	33 (54.1%)	

The above table shows the Educational status of the study population. 45.9% of the total study population had education up to primary level and 54.1% of them had education more than primary (i.e., secondary & above).

The difference between the two groups was statistically not significant.

Table - 6: Employment status of the sample:

Employment status	With metabolic syndrome (n=30)	Without metabolic syndrome (n=31)	Total (n=61)	Statistical inference
Working	19 (63.3%)	21 (67.7%)	40 (65.6%)	X^2=.131 Df=1 .717>0.05 Not Significant
Not working	11 (36.7%)	10 (32.3%)	21 (34.4%)	

The above table describes the distribution of study population according to their employment status. Total number of persons employed in the sample was 40 (65.6%) and around 21 persons were unemployed (34.4%).

No significant differences were made out between the two groups.

Table - 7: Locality of the sample:

Locality	**With metabolic syndrome** ***(n=30)***	**Without metabolic syndrome** ***(n=31)***	**Total** ***(n=61)***	**Statistical inference**
Rural	24 (80.0%)	24 (77.4%)	48 (78.7%)	X^2=.061 Df=1 .806>0.05 Not Significant
Urban	6(20.0%)	7 (22.6%)	13 (21.3%)	

The above table illustrates the distribution of sample based on their location. Among the sample 78.7% of patients were from rural background and 21.3% were from urban areas.

The difference between the two groups based on their location was not statistically significant.

Table - 8: Marital status of the sample:

Marital status	**With metabolic syndrome *(n=30)***	**Without metabolic syndrome *(n=31)***	**Total *(n=61)***	**Statistical inference**
Married	26 (86.7%)	23 (74.2%)	49 (80.3%)	X^2=12.171 Df=2 .002<0.05 **Significant**
Unmarried	0 (0%)	8 (25.8%)	8 (13.1%)	
Widow	4 (13.3%)	0 (.0%)	4 (6.6%)	

The above table shows the marital status of the sample.80.3% of the study population were married.13.1% were unmarried and they belong to Bipolar disorder patients without metabolic syndrome. 6.6% of the study population were widows and they belong to Bipolar disorder with metabolic syndrome. The difference between the two groups was statistically significant.

FIGURE 3: MARITAL STATUS.

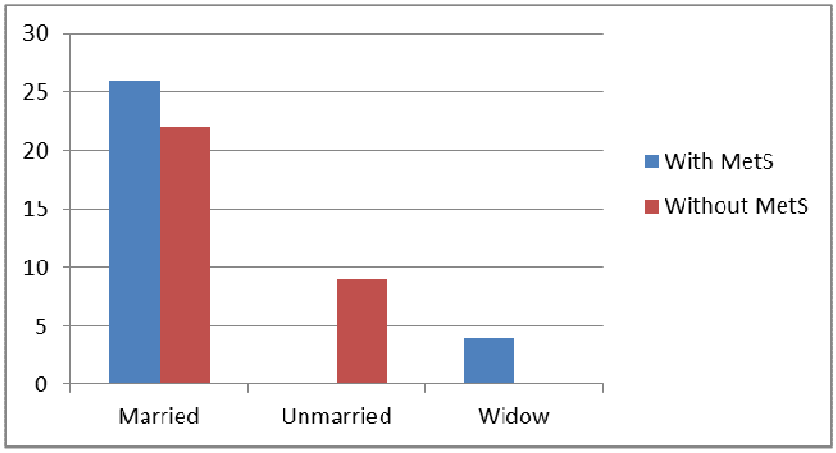


Table - 9: Dietary habits:

Diet	**With metabolic syndrome** ***(n=30)***	**Without metabolic syndrome** ***(n=31)***	**Total** ***(n=61)***	**Statistical inference**
Veg	2 (6.7%)	4 (12.9%)	6 (9.8%)	X^2=.669 Df=1 .414>0.05 Not Significant
Non-Veg	28 (93.3%)	27 (87.1%)	55 (90.2%)	

The above table shows that around 90.2% of the study population were taking non vegetarian diet and around 9.8% people were taking vegetarian diet.

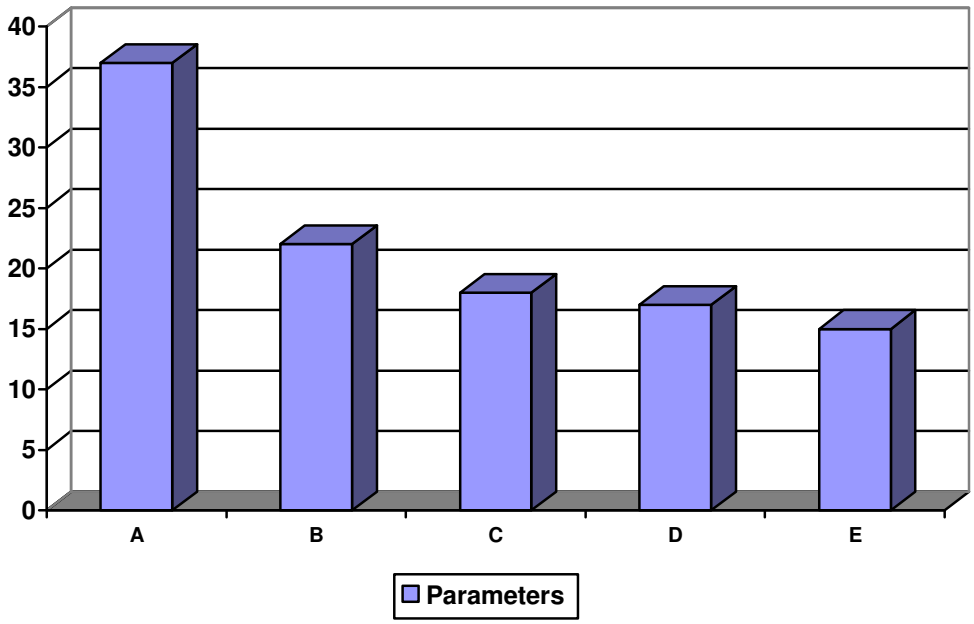
The difference between the two groups was not statistically significant.

Table: 10: Distribution of components of metabolic syndrome in sample:

Parameters	Numbers (n)	Percentage (%)
Abnormal waist circumference	37	60.65
Reduced HDL	22	35.3
Increased triglyceride	18	29.5
Increased BP	17	27.3
Increased FBS	15	24.59

The above table shows the distribution of abnormal metabolic parameters in the total sample population. Waist circumference was the most common parameter altered and fasting sugar was the least common. Out of total 61 patients thirty patients (49.18%) met the criteria for metabolic syndrome.

FIGURE : 4 DISTRIBUTION OF COMPONENTS OF METABOLIC SYNDROME



A - Abnormal waist circumference

B - Reduced HDL

C - Increased triglyceride

D - Increased BP

E - Increased FBS

Table - 11: Anthropometric parameters of the sample:

Anthropometric Parameters n(61)	Minimum	Maximum	Mean	SD
WC(cm)	68	105	87.08	8.582
BMI	18	31	24.18	3.462

The above table shows the distribution of anthropometric parameters in the study population. The maximum waist circumference recorded in our sample was 105 cm and the minimal measurement was 68 cm. The average waist circumference of the total study population was 87.08±8.528.

The average Body mass index of the total sample was 24.18±3.462.

Table - 12: Biochemical parameters of the sample:

Biochemical parameters n(61)	Minimum	Maximum	Mean	SD
FBS(mg/dl)	68	119	96.43	14.151
PPBS(mg/dl)	100	147	131.05	11.322
HDL(mg/dL)	33	60	46.89	6.726
TG(mg/dL)	115	158	142.30	10.364

The above table illustrates the distribution of biochemical parameters in the study population. The average fasting blood sugar of the sample was 96.43±14.151 and the postprandial blood sugar was 131.05±11.322. The lowest High Density Lipoprotein (HDL) value recorded was 33 with an average of 46.89±6.726. The mean Triglyceride (TG) value of the sample was 142.30±10.364.

Table – 13: Thyroid profile of the sample:

Thyroid profile n(61)	Minimum	Maximum	Mean	SD
FT3	3	5	3.41	.580
FT4	1	2	1.20	.345
TSH	1	6	3.20	1.632

The above table shows the distribution of thyroid profile in the total study population. On an average the free T3 in the sample was 3.14±0.580, free T4 was found to be 1.20±0.345. The average TSH value of the sample was 3.20±1.632.

Table - 14: Alcohol use in the sample:

Alcohol use	**With metabolic syndrome** ***(n=30)***	**Without metabolic syndrome** ***(n=31)***	**Total** ***(n=61)***	**Statistical inference**
Yes	16 (53.3%)	11 (35.5%)	27 (44.3%)	X^2=1.969 Df=1 .161>0.05 Not Significant
No	14 (46.7%)	20 (64.5%)	34 (55.7%)	

The above table shows the alcohol consumption in the study population. Around 27 (44.3%) persons in the sample were taking alcohol. Out of them 16 persons (53.3%) qualified for metabolic syndrome. No significant differences between the two groups were made out in statistical analysis.

Table - 15: Alcohol abuse in the sample:

Alcohol Abuse	Mean	S.D	t	Df	Statistical inference
With Metabolic Syndrome (N=30)	1.69	.479	1.690	25	.103>0.05 Not Significant
Without Metabolic Syndrome (N=31)	1.36	.505			

The above table shows the alcohol abuse pattern in the total study population. On an average Bipolar disorder patients with metabolic syndrome had a mean of 1.69±0.479 and those without metabolic syndrome had a mean of 1.36±0.505. The distribution was almost same for both groups and hence the difference was statistically not significant.

Table - 16: Alcohol dependence in the sample:

Alcohol Dependence	Mean	S.D	t	df	Statistical inference
With Metabolic Syndrome (N=30)	1.56	.512	-.850	25	.403>0.05 Not Significant
Without Metabolic Syndrome (N=31)	1.73	.467			

The above table shows the alcohol dependence pattern in the total study population. On an average Bipolar disorder patients with metabolic syndrome had a mean of 1.56±0.512 and those without metabolic syndrome had a mean of 1.73±0.467. The distribution was almost same for both groups and hence the difference was statistically not significant

Table - 17: Index episode of the sample:

Index episode	**With metabolic syndrome** ***(n=30)***	**Without metabolic syndrome** ***(n=31)***	**Total** ***(n=61)***	**Statistical inference**
Mania	21 (70.0%)	27 (87.1%)	48 (78.7%)	X^2=2.668 Df=2 .263>0.05 Not Significant
Depression	7 (23.3%)	3 (9.7%)	10 (16.4%)	
Mixed	2 (6.7%)	1 (3.2%)	3 (4.9%)	

The above table shows the nature of the index episode of the study population. Majority had Mania as the first episode (n=48; 78.7%) followed by depressive episodes (n=10; 16.4%).

The difference between the two groups was not statistically significant.

FIGURE 6: INDEX EPISODE.

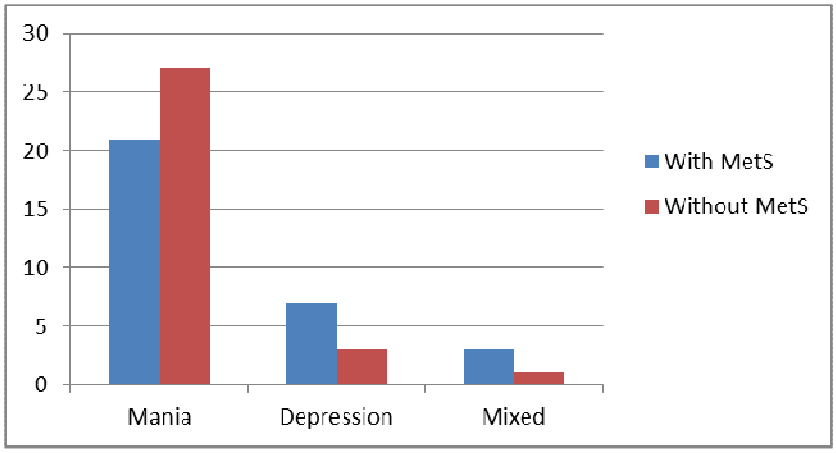


Table - 18: Total number of lifetime episodes:

	Mean	**S.D**	**T**	**Df**	**Statistical inference**
With Metabolic Syndrome (N=30)	6.47	1.224	6.844	59	.000<0.05 **Significant**
Without Metabolic Syndrome (N=31)	4.13	1.432			

The above table illustrates the total number of lifetime episodes in the study population. On an average Bipolar disorder patients with metabolic syndrome had a mean of 6.47 and those without metabolic syndrome had a mean of 4.13 lifetime episodes.

The difference between the two groups was statistically significant.

FIGURE 7: TOTAL NO. OF EPISODES

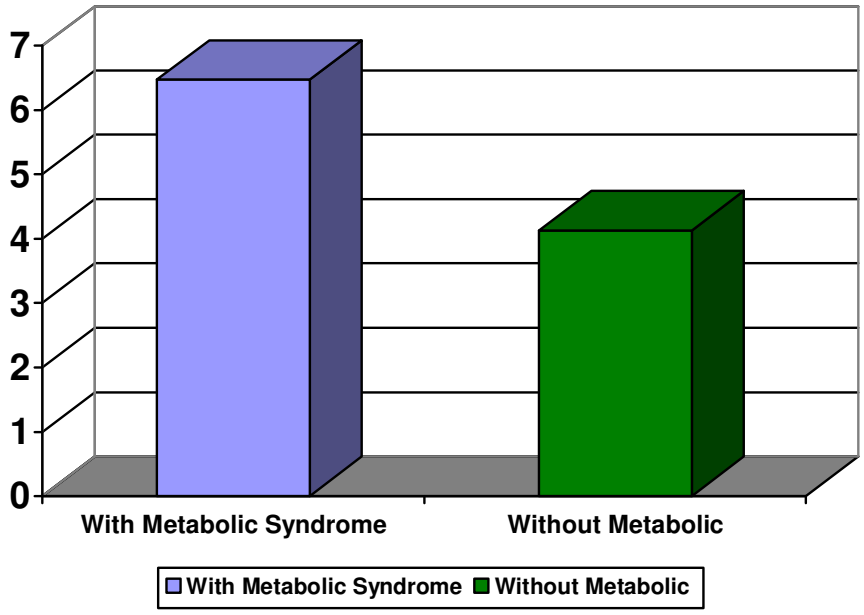


Table - 19: Total number of lifetime manic episodes:

	Mean	**S.D**	**t**	**Df**	**Statistical inference**
With Metabolic Syndrome (N=30)	3.57	1.194	3.219	59	.002<0.05 **Significant**
Without Metabolic Syndrome (N=31)	2.71	.864			

The above table shows the total number of lifetime manic episodes in the study population. On an average Bipolar disorder patients with metabolic syndrome had a mean of 3.57 and those without metabolic syndrome had a mean of 2.71 lifetime manic episodes.

The difference between the two groups was statistically significant.

Table - 20: Total number of lifetime depressive episodes:

	Mean	**S.D**	**t**	**Df**	**Statistical inference**
With Metabolic Syndrome (N=30)	2.70	1.557	4.110	59	.000<0.05 **Significant**
Without Metabolic Syndrome (N=31)	1.23	1.230			

The above table shows the total number of lifetime depressive episodes in the study population. On an average Bipolar disorder patients with metabolic syndrome had a mean of 2.70 and those without metabolic syndrome had a mean of 1.23 lifetime depressive episodes.

The difference between the two groups was statistically significant.

Table - 21: Total number of lifetime mixed episodes:

	Mean	S.D	t	Df	Statistical inference
With Metabolic Syndrome (N=30)	.20	.484	.049	59	.961>0.05 Not Significant
Without Metabolic Syndrome (N=31)	.19	.543			

The above table shows the total number of lifetime mixed episodes in the study population. On an average Bipolar disorder patients with metabolic syndrome had a mean of 0.20 and those without metabolic syndrome had a mean of 0.19 lifetime mixed episodes.

The difference between the two groups was statistically not significant.

Table - 22: Age at onset of Bipolar disorder:

Age at onset	Mean	S.D	t	df	Statistical inference
With Metabolic Syndrome (N=30)	25.23	2.112	.260	59	.796>0.05 Not Significant
Without Metabolic Syndrome (N=31)	25.06	2.886			

The above table illustrates the age of onset of Bipolar disorder in the study population. The age at onset of the illness in Bipolar disorder patients with metabolic syndrome was found to be 25.23±2.112 and for those without metabolic syndrome was 25.06±2.886.

The difference between the two groups was not statistically significant.

FIGURE 8: AGE AT ONSET.

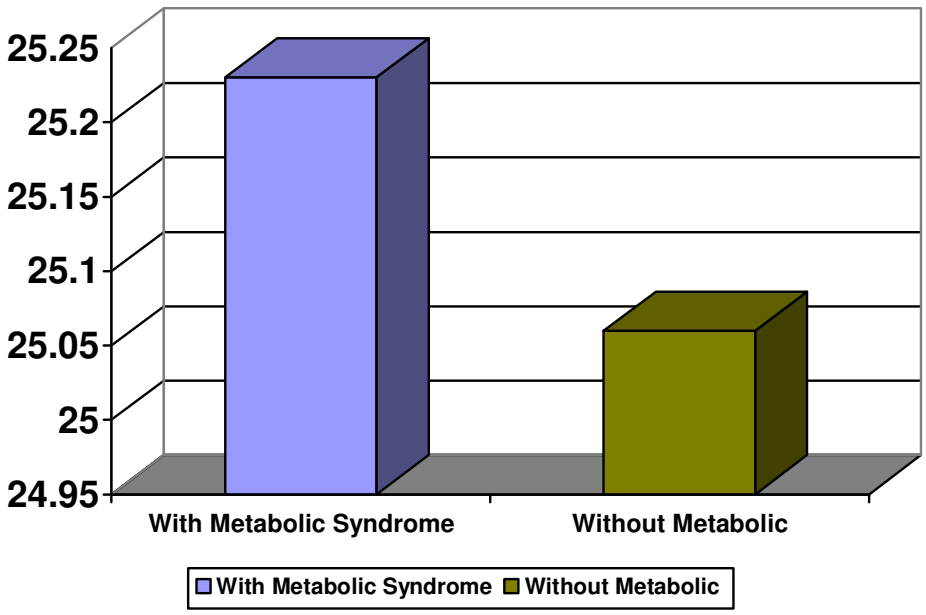


Table - 23: Nature of the current episode:

current episode	**With metabolic syndrome** ***(n=30)***	**Without metabolic syndrome** ***(n=31)***	**Total** ***(n=61)***	**Statistical inference**
Mania	14 (46.7%)	20 (64.5%)	34 (55.7%)	X^2=1.969 Df=1 .161>0.05 Not Significant
Depression	16 (53.3%)	11 (35.5%)	27 (44.3%)	

The above table depicts the nature of the current episode in the study population. Majority had manic episodes (55.7%). Around 27 (44.3%) persons had depressive episodes. No mixed episodes have been reported.

The difference between the two groups was statistically not significant.

FIGURE 9: CURRENT EPISODE.

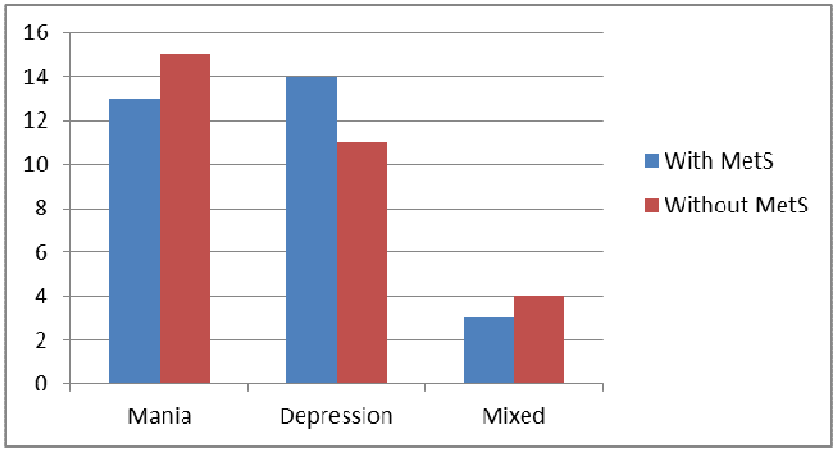


Table - 24: Comparison of Young Mania Rating Scale total scores between Bipolar disorder with metabolic syndrome and Bipolar disorder without metabolic syndrome:

YMRS	Mean Total YMRS scores	S.D	T	df	Statistical inference
With Metabolic Syndrome (N=30)	6.87	7.628	-2.693	59	.009<0.05 **Significant**
Without Metabolic Syndrome (N=31)	13.06	10.129			

This table shows that mean total YMRS scores are higher in Bipolar disorder patients without metabolic syndrome (13.06±9.10.129) compared to those with metabolic syndrome (6.87±7.628).

The difference between the two groups was statistically significant

FIGURE 10: COMPARISON YOUNG MANIA RATING SCALE TOTAL SCORES

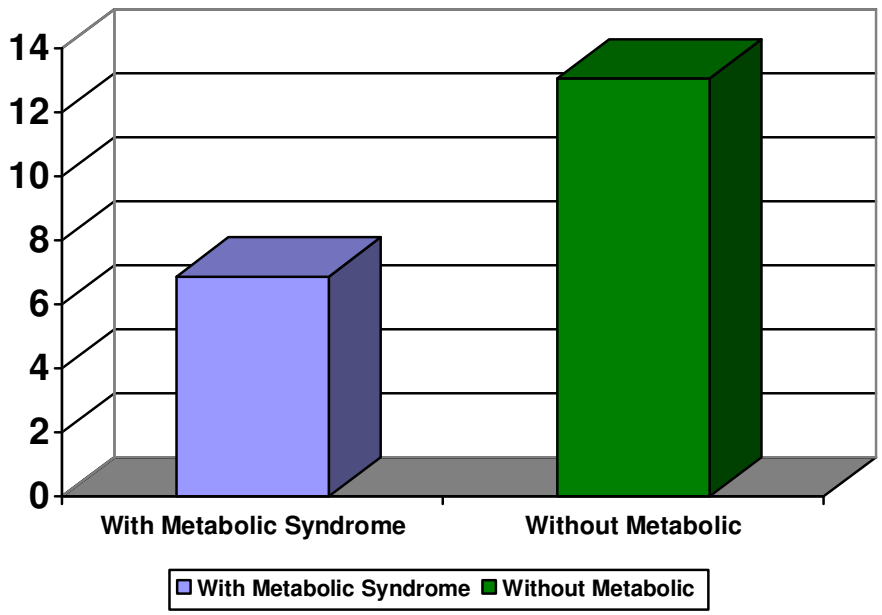


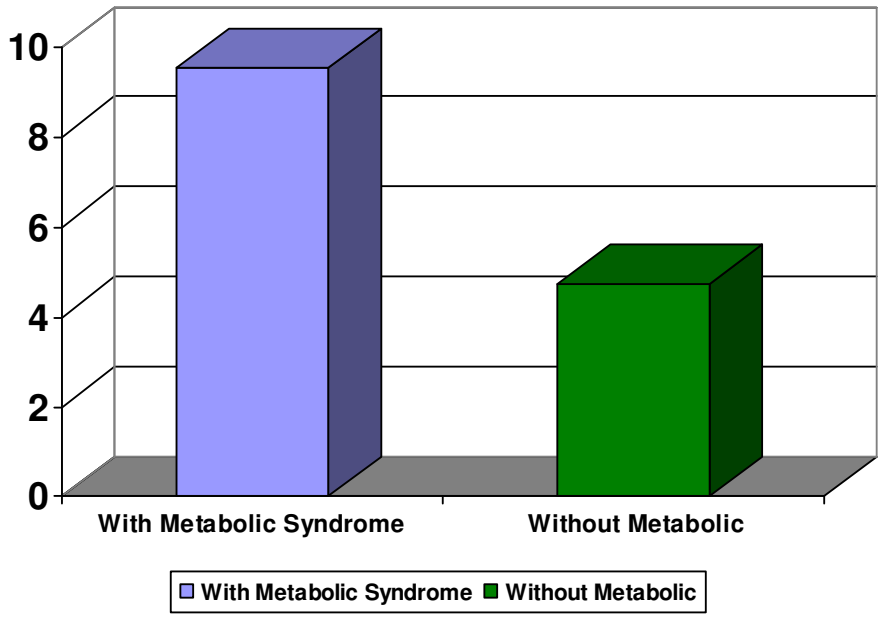
Table - 25: Comparison of Hamilton Depression Rating Scale total scores between Bipolar disorder with metabolic syndrome and Bipolar disorder without metabolic syndrome:

HAMD	Mean Total HAMD scores	S.D	T	Df	Statistical inference
With Metabolic Syndrome (N=30)	9.53	9.261	2.361	59	.022<0.05 **Significant**
Without Metabolic Syndrome (N=31)	4.71	6.497			

This table shows that mean total HAMD scores are higher in Bipolar disorder patients with metabolic syndrome (9.53±9.261) compared to those without metabolic syndrome (4.71±6.497).

The difference between the two groups was statistically significant.

FIGURE 11: COMPARISON HAMILTON DEPRESSION RATING SCALE TOTAL SCORES



DISCUSSION

In the present study we examined 61 patients with the diagnosis of Bipolar disorder who attended department of psychiatry of Thanjavur medical college hospital. We conducted a detailed physical examination and clinical assessment. Patients were assessed for the metabolic abnormalities like obesity, hypertension, diabetes mellitus, dyslipidemia, and thyroid functions. Our aim was to assess the extent to which these metabolic abnormalities are present in the given sample and delineate as to how many of them qualify for a diagnosis of metabolic syndrome. In addition we wanted to discern the relationship between metabolic syndrome and the severity of the present state as well as the course variables of Bipolar disorder.

Studies from west have concluded that the metabolic syndrome and its components are interwoven with the disease progression and appear to be powerful determinants of the course of Bipolar disorder.[24, 58] The linkages between metabolic syndrome and Bipolar disorder have not been explored in Indian context despite growing rates of early onset of diabetes mellitus and hypertension. In the present study in addition to examining the prevalence of metabolic syndrome in Bipolar patients an effort has been made to explore its relationship with the type of index episode, total numbers of life time episodes, and severity of the current episode. This particular aspect hasn't received attention in the Indian context.

SOCIODEMOGRAPHIC VARIABLES

AGE AND METABOLIC SYNDROME IN BIPOLAR DISORDER

The patients of Bipolar disorder with Metabolic syndrome were found to be much older than patients with Metabolic syndrome alone.[145,155,156,157] A review of 34 studies[24] across the world shows prevalence ranging from 16.7 to 67% with a mean age ranging from 34.1 to 55.7 years. A recent meta-analytic investigation[58] (33 studies, N=6,286) revealed that the prevalence of Metabolic syndrome across studies was 37.3% with a mean age of 42.8 years. Study by Grover et al, which was the first of its kind regarding this aspect in Indian context, reported a prevalence of 41% metabolic syndrome in patients of Bipolar disorder with mean age of 39 years. In our study the mean age of patients of Bipolar disorder with Metabolic syndrome is 46.77±6.07 years as compared to these Bipolar patients without Metabolic syndrome (33.29±9.4 years) and the prevalence was 49.18%. These findings are consistent with the existing literature.

GENDER AND METABOLIC SYNDROME IN BIPOLAR DISORDER

Studies which analysed the age adjusted prevalence[158, 159] of Metabolic syndrome with regard to gender in Bipolar disorder give variable findings. The prevalence of metabolic syndrome was less in European women as compared to

men (14.4%Vs 18.4%), while South Asian men were having lesser rate of metabolic syndrome as compared to women (28.8%Vs 31.8%). Studies conducted in United States also show a higher prevalence of Metabolic syndrome in women (23.7% Vs 15.7%). Grover et al[24] in his study reported that 61 men and 21 women satisfied the modified NCEP ATP-III criteria,[49] which thus showed the prevalence of metabolic syndrome was higher in men (43.57% Vs 35%). In our study 16 men and 14 women met the criteria (53.34% Vs 46.67%) for metabolic syndrome showing a higher prevalence of metabolic syndrome in men than in women which is in tune with the above Indian study.

Other socio-demographic variables like religious background, employment status and place of stay were quite comparable to those reported by Grover et al.[24]

PREVALENCE OF METABOLIC ABNORMALITIES

OBESITY

Overweight, obesity and extreme obesity were found to be common in patients with Bipolar disorder[12].The prevalence of overweight and obesity in the patient of Bipolar disorder is reported[18] to be 20-35%. Majority of the studies use the Body Mass Index (BMI) >30 as cut off to define obesity while in our study we define obesity when the BMI >25 and overweight when the BMI>23.

This is based on the modified criteria of obesity for Asian population by WHO.[10] Studies done in the west[24] report that BMI ranges between 30.4 and 46.5. Grover S et al.[160] reported that the average BMI was 25.91 among Bipolar disorder patients and it was higher in women compared to men. While the average BMI in our sample was 24.18. It was similar to the above mentioned study.

The waist circumference (WC) is the measurement of abdominal fat and an easily measurable component of metabolic syndrome. High waist circumference is seen commonly in Bipolar patients as compared to age matched control group.[7] In their review Grover et al[24] report that the prevalence of waist circumference ranges 30% to 61% among Bipolar disorder patients. There was a higher prevalence in the present study (60.65%) with waist circumference being more among men compared to women. While BMI offers the best estimate of total body fat, waist circumference gives an estimate of visceral fat and risk of obesity related diseases.

Studies suggest that high BMI is associated with greater number of lifetime depressive and manic episodes and difficult to treat index episode, in addition to a high recurrence rate for depressive episodes.[5] In our study we did not find a significant correlation between the higher BMI and the total numbers of life time episodes but there was a strong correlation between waist circumference and the number of mixed episodes. However the number of

patients with mixed episode was not high in the sample and this finding is merely an indicative one. There was also a correlation between age and waist circumference (p=0.016) with older patient having more abdominal fat.

HYPERTENSION

Patients with Bipolar disorder have a high prevalence of hypertension and increased risk of mortality due to cardiovascular disease.[17-19] In their review Grover et al[24] report that the prevalence of hypertension in patients of Bipolar disorder ranges from 18.6% to 78.1%. In the present study 27.3% patients were hypertensive which is within the range reported in the literature. However the role of antihypertensive medications in modulating the prevalence has to be taken into consideration.

DYSLIPIDEMIA

Studies across the world show a high prevalence of dyslipidemia in patients of Bipolar disorder.[7] In a recent review of 34 studies Grover et al[24] report that the prevalence of low HDL level across the 19 studies was ranging from 21.7% to 67.6% and high triglyceride range from 22.7% to 58.8%. In the present study 35.3% of patients were having low HDL level while 29.50% were having high triglyceride level. These findings are again consistent with the previous studies.

DIABETES MELLITUS

Impaired glucose tolerances and insulin resistance is found to be more common in individuals with Bipolar disorder than in the general population.[31] Grover et al[24] reported that the prevalence of high fasting blood sugar across 19 studies ranges from 6% to 32.4%. In the present study 24.59% patients were having high FBS which is in tune with the findings in the literature.

THYROID ABNORMALITIES

In view of the extensive metabolic effect of thyroid hormone and its close relation with mood disorders[41] we examined thyroid functions and found that higher TSH level (>5mU/mL) was seen in 28% patients. Overt or subclinical hypothyroidism has been associated with metabolic risk factors, including cardiovascular disease and dyslipidemia.[42-45] Abnormal thyroid function also has been linked to slower response to acute treatment and poor quality of long term remission in Bipolar patients.[46]

PREVALENCE OF METABOLIC SYNDROME

Metabolic syndrome, which is a constellation of metabolic abnormalities, associated with development of coronary heart disease,[48,49] as the available data suggest that cardiovascular disease is the most common cause of excess and premature mortality in Bipolar disorder patients.[17-19] Prevention, identification, and modification of the cardiovascular risk factors should be one of the

important therapeutic objectives in the managements of Bipolar disorder. The studies across different countries[24] reported the prevalence of metabolic syndrome in the range of 16.7% to 67%. The study from India revealed a prevalence of 41%. Present study gives a prevalence of 49.18 % which fall within the range.

COMPONENTS OF METABOLIC SYNDROME

Metabolic syndrome comprises of both anthropometric and metabolic parameters. Studies from the West indicate waist circumference (WC) to be the most common abnormality[24] (30- 85%) with high fasting blood sugar (FBS) being least common (6-43.5%), Lipid abnormalities were intermediate in prevalence. In the present study abnormal waist circumference was seen in 60.65% patients (n=37) followed by low HDL level (35.3%), high triglyceride (29.50%), high blood pressure (27.3%) with high fasting blood sugar (FBS) being least common 24.59% . Unlike Grover.S et al.[160] study which reported high blood pressure to be the second most common metabolic parameter in metabolic syndrome, in the present investigation increased triglyceride and low HDL were more prevalent than increased blood pressure. These findings indicate that there could be variations across and within nations.

CLINICAL COREELATES OF METABOLIC SYNDROME IN BIPOLAR DISORDER

Metabolic syndrome has an impact on the course of Bipolar disorder. Presence of metabolic syndrome is reported to be associated with greater numbers of manic and depressive episodes.[146,6] longer duration of illness,[144,145] more frequent Bipolar I disorder,[144] more frequent depressive episode at onset,[147] difficult to treat index episodes[146,6] and lesser severity of index manic episode.[156] Lag period to treatment was more among patients with metabolic syndrome .[149] An attempt was made in the present investigation to explore the association of salient clinical variables with metabolic syndrome . It was found that patients of Bipolar disorder with metabolic syndrome had more number of total life time episodes as compared with the patients without metabolic syndrome (6.47±1.2 Vs 4.13±1.4), a longer duration of illness (15.36 Vs 10.16 yrs), and a greater frequency of type I Bipolar disorder. These patients reported a higher frequency of depressive episode at onset of illness (23.3% Vs 9.7%). In addition the severity of current episode as assessed by the relevant scales showed that depressive episodes were more severe (9.53±9.261 Vs 4.71±6.497) and manic episodes were of lesser severity (6.87±7.628 Vs 13.06±10.129). The lag period to treatment among patients with metabolic syndrome was found to be longer (82.9±221 Vs 63.9±260). These findings of clinical correlates of metabolic syndrome in Bipolar disorder are consistent with the previous studies.

In addition to the above clinical correlates, in the present study the frequency of depressive episodes were found to be significantly higher in the patients with Bipolar disorder with metabolic syndrome (2.7±1.5Vs 1.23±1.23; p=0.008). The interplay between depression and metabolic syndrome is mediated through multiple mechanisms and a bidirectional association is most likely.

SUBSTANCE USE AND METABOLIC SYNDROME IN BIPOLAR DISORDER

Substance abuse disorders had been demonstrated to have higher incidence in Bipolar disorder patients than in general population. In general population the incidence was 12.8%; but in Bipolar disorder it is shown to be significantly higher at 35.3% (108) (NESARC; study on 43093 respondents). They also demonstrated the 12-month prevalence of substance use disorders, which was about 27.9% in mania patients and 26.6% in hypomania; but the same was only 9.4% in the general population (108).

In another study (109) on Bipolar disorder patients nicotine dependency was significantly higher at 70%; and use / abuse of alcohol was also greater than the general population. In another study the alcohol use in Bipolar disorder patients was reported to be 21.4 to 54.5% (110).

In the present study we found that 27 patients (44.37%) had history of alcohol use, with 10 patients (16.4%) being dependent on it. All alcohol users were also found to use nicotine in various forms. We did not find any

association between substance use, abuse and dependence with metabolic syndrome in the present sample. On the other hand increased triglyceride level (p=0.013) increased total cholesterol (p=0.044), and increased systolic blood pressure (p=0.039), were common among alcohol users.

PREDICTORS OF METABOLIC SYNDROME IN BIPOLAR DISORDER

Multiple factors affect the occurrence of metabolic syndrome in Bipolar patients. Western studies suggest that longer duration illness[144,145] and age more than 35 years can be a strong predictor for the development of metabolic syndrome , which has been replicated by Grover et al[160] in the Indian context. A binary logistic regression analysis was carried out to identify predictors of metabolic syndrome in the present study. Age, number of lifetime depressive episodes and more total number of lifetime episodes are significant predictors.

CONCLUSIONS

The present study is a cross sectional study done on 61 patients with a diagnosis of Bipolar Affective Disorder with a view to examine the presence of Metabolic Syndrome and its clinical correlates. The study was conducted in a general hospital psychiatric unit.

A detailed clinical history was taken using a life chart. Anthropometric measurements were taken, relevant biochemical investigations to assess metabolic changes were done and the severity of the current clinical episode was assessed using relevant scales.

The study findings revealed that:

1. The mean age of the study population was 39 years. More than half of them were males, majority of them being from rural areas, educated up to secondary level. Half of the population were employed, with women being mainly housewives. Majority were Hindus.
2. The prevalence of metabolic syndrome was 49.18% in the given sample.
3. Waist circumference was the most common abnormal anthropometric parameter in these patients (60.65%).
4. Low HDL level was seen in 35.3%.
5. High triglyceride level was found in 29.5%.
6. High blood pressures were recorded in 27.3% with high fasting blood sugars in 24.59%.

7. The use of alcohol was significantly associated with various metabolic abnormalities like increased triglyceride (p=0.013), increased total cholesterol (p=0.044), and increased systolic blood pressure (p=0.039).
8. Patients of Bipolar disorder with metabolic syndrome were found to have a greater number of life time episodes, longer duration of illness, more frequent association of Bipolar type I disorder, onset of illness with a depressive episode, greater numbers of lifetime depressive episodes (p=0.008) more severe index depressive episode and a lesser severity of index manic episode.
9. Age of the patients, number of lifetime depressive episodes and more total number of lifetime episodes were found to be associated with the development of metabolic syndrome.

SUMMARY

The Metabolic syndrome has a strong association with Bipolar disorder, with an adverse effect on the course of the illness. The main components of the metabolic syndrome can be detected and modified easily. Early identification and intervention for the same could affect the course of Bipolar disorder favourably as well as reduce the mortality and morbidity associated with it. The present study is carried out with the objectives to examine the extent and the impact of metabolic syndrome on Bipolar disorder.

A cross sectional study was done on 61 consecutive patients with a diagnosis of Bipolar Affective Disorder, attending the psychiatry department, Thanjavur medical college hospital, recruited by purposive sampling method for a period of six months.

The patients were screened for various anthropometric and metabolic abnormalities by using standard methods. The severity of the present symptoms was assessed by appropriate rating scales. The diagnosis of metabolic syndrome was derived by adopting a standardized consensus definition.

The mean age of the study population was 39 years. More than half of them were males, majority of them being from rural areas, educated up to secondary level. Half the population were employed, with women being mainly housewives. Majority were Hindus.

The criteria for the metabolic syndrome were satisfied by 49.18% of patients. The prevalence was seen to increase with age, and was higher in the male patients. The various components of metabolic syndrome were also found to be high. 64% patients were obese, 60.65% were having abdominal obesity, hypertension was present in 27.3%, low HDL found in 35.3%, increased triglyceride present in 29.5%, and increased fasting blood sugar was present in 24.59%. 44.3% were using alcohol. Thyroid function abnormalities were detected in 28%. Patients with increased abdominal obesity were found to have more mixed episodes (p=0.015).

Patients of Bipolar disorder with metabolic syndrome were found to have a greater number of lifetime episodes, longer duration of illness, more frequent depressive episodes at onset, and a more severe index depressive episode. The lag period to treatment was more and the index manic episode was of lesser severity. The life time depressive episodes were significantly higher in them (p=0.008).

Increasing age, more number of lifetime depressive episodes and the more total number of lifetime episodes appear to be predictors for the occurrence of metabolic syndrome in patients with Bipolar disorder. We thus have valuable

insight about the relationship between metabolic syndrome and Bipolar disorder. The presence of metabolic syndrome influences the course and severity of the illness. It is possible to detect the presence of the metabolic syndrome and its components in the early stages of their development and plan timely intervention. This would help in altering the course and severity of the illness in a favourable manner.

IMPLICATIONS

1. Considering the high prevalence of metabolic syndrome in the patients of Bipolar disorder, strategies have to be developed for prevention, early detection and treatment of the same.
2. Patients need to be assessed on risk factors for a metabolic syndrome based on family history, personal history, relevant anthropometric measurements and biochemical investigations.
3. Appropriate psychoeducation regarding a healthy lifestyle, physical activity, and a healthy diet, can be provided to all the patients as a regular protocol which can prevent the occurrence of metabolic syndrome.

LIMITATIONS

1. The current study being a cross sectional one in design, has its own limitations. The sample size being small, and the study being based in a general hospital setting, makes generalization difficult.
2. Recall biases may affect the precision of information about the previous episodes, especially medication details.
3. Lack of control group makes it difficult to comment about the effect of psychosocial factors.

STRENGTH OF THE STUDY

1. The present study has covered some of the issues that the previous studies have not examined.
2. The effects of substance use, and the correlation of the metabolic syndrome with the clinical presentation of Bipolar disorder, have been looked into.
3. The association of clinical variables impacting metabolic syndrome in Bipolar patients hasn't received adequate attention in the Indian context.
4. By demonstrating their significant associations of metabolic syndrome, the present investigation sets the stage for further specific enquiries into this important area.

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ANNEXURE - I

Consent form:

தகவல் அறிந்து ஆய்வில் பங்கேற்பதற்கான ஒப்புதல்:

…….. ஆகிய நான் மனசோர்வு / மனஎழுச்சி நோய் மற்றும் வளர்சிதை மாற்ற நோய்க்குறி இடையிலான தொடர்பை அறிவதற்கான ஆய்வில் பங்கேற்க முழு மனதுடன் சம்மதிக்கிறேன்,

இந்த ஆய்வின் நோக்கத்தை மருத்துவரிடமிருந்து அறிந்து கொண்டேன். நான் அளிக்கும் தகவல்கள் ரகசியமாக காக்கப்படும் என்று அறிவேன்.

எனக்கு விருப்பமில்லையெனில் எந்த நேரத்திலும் விலகிக்கொள்ளலாம் என்று அறிவேன்,

மருத்துவரின் கையொப்பம் நோயாளி / காப்பாளரின் கையொப்பம்

தேதி:

முகவரி:

ANNEXURE – II

Patient's Socio-Demographic & Clinical Profile:

1. Age: .....years

2. Sex: Male / Female

3. Education:

4. Occupation: Employed / Unemployed

5. Marital status: Married / Never married / Separated-Divorced / Widow

6. Locality : Rural / Urban

7. Dietary Habit: Veg / Non-veg / Egg

Patient's clinical profile:

1. Age at onset
2. Nature of the Index episode: Mania/ Depression/Mixed
3. Total number of lifetime episodes
4. Total number of lifetime manic episodes
5. Total number of lifetime depressive episodes
6. Total number of lifetime mixed episodes
7. Nature of the current episode: Mania/ Depression/Mixed
8. Severity of the current episode:
   YMRS total score(in Mania):
   HAMD total score(in Depression):
9. Alcohol use: use/abuse/dependence

ANNEXURE – III

YOUNG MANIA RATING SCALE (YMRS)

1. Elevated Mood
0 Absent
1 Mildly or possibly increased on questioning
2 Definite subjective elevation; optimistic, self-confident; cheerful; appropriate to content
3 Elevated; inappropriate to content; humorous
4 Euphoric; inappropriate laughter; singing

2. Increased Motor Activity-Energy
0 Absent
1 Subjectively increased
2 Animated; gestures increased
3 Excessive energy; hyperactive at times; restless (can be calmed)
4 Motor excitement; continuous hyperactivity (cannot be calmed)

3. Sexual Interest
0 Normal; not increased
1 Mildly or possibly increased
2 Definite subjective increase on questioning
3 Spontaneous sexual content; elaborates on sexual matters; hypersexual by self-report
4 Overt sexual acts (toward patients, staff, or interviewer)

4. Sleep
0 Reports no decrease in sleep
1 Sleeping less than normal amount by up to one hour
2 Sleeping less than normal by more than one hour
3 Reports decreased need for sleep
4 Denies need for sleep

5. Irritability
0 Absent
2 Subjectively increased
4 Irritable at times during interview; recent episodes of anger or annoyance on ward
6 Frequently irritable during interview; short, curt throughout
8 Hostile, uncooperative; interview impossible

6. Speech (Rate and Amount)
0 No increase
2 Feels talkative
4 Increased rate or amount at times, verbose at times
6 Push; consistently increased rate and amount; difficult to interrupt
8 Pressured; uninterruptible, continuous speech

7. Language-Thought Disorder
0 Absent
1 Circumstantial; mild distractibility; quick thoughts
2 Distractible, loses goal of thought; changes topics frequently; racing thoughts
3 Flight of ideas; tangentiality; difficult to follow; rhyming, echolalia
4 Incoherent; communication impossible

8. Content
0 Normal
2 Questionable plans, new interests
4 Special project(s); hyper-religious
6 Grandiose or paranoid ideas; ideas of reference
8 Delusions; hallucinations

9. Disruptive-Aggressive Behaviour
0 Absent, cooperative
2 Sarcastic; loud at times, guarded
4 Demanding; threats on ward
6 Threatens interviewer; shouting; interview difficult
8 Assaultive; destructive; interview impossible

10. Appearance
0 Appropriate dressing and grooming
1 Minimally unkempt
2 Poorly groomed; moderately dishevelled; overdressed
3 Dishevelled; partly clothed; garish make-up
4 Completely unkempt; decorated; bizarre garb

11. Insight
0 Present; admits illness; agrees with need for treatment
1 Possibly ill
2 Admits behaviour change, but denies illness
3 Admits possible change in behaviour, but denies illness
4 Denies any behaviour change

ANNEXURE – IV

HAMILTON RATING SCALE FOR DEPRESSION (HAM-D)

For each item, write the correct number on the line next to the item. (Only one response per item)

1. DEPRESSED MOOD (Sadness, hopeless, helpless, worthless)
0= Absent
1= These feeling states indicated only on questioning
2= These feeling states spontaneously reported verbally
3= Communicates feeling states non-verbally—i.e., through facial expression, posture, voice, and tendency to weep
4= Patient reports VIRTUALLY ONLY these feeling states in his spontaneous verbal and non-verbal communication

2. FEELINGS OF GUILT
0= Absent
1= Self reproach, feels he has let people down
2= Ideas of guilt or rumination over past errors or sinful deeds
3= Present illness is a punishment. Delusions of guilt
4= Hears accusatory or denunciatory voices and/or experiences threatening visual Hallucinations

3. SUICIDE
0= Absent
1= Feels life is not worth living
2= Wishes he were dead or any thoughts of possible death to self
3= Suicidal ideas or gesture
4= Attempts at suicide (any serious attempt rates 4)

4. INSOMNIA EARLY
0= No difficulty falling asleep
1= Complains of occasional difficulty falling asleep—i.e., more than 1/2 hour
2= Complains of nightly difficulty falling asleep

5. INSOMNIA MIDDLE
0= No difficulty
1= Patient complains of being restless and disturbed during the night
2= Waking during the night—any getting out of bed rates 2 (except for purposes of voiding)

6. INSOMNIA LATE
0= No difficulty
1= Waking in early hours of the morning but goes back to sleep
2= Unable to fall asleep again if he gets out of bed

7. WORK AND ACTIVITIES
0= No difficulty
1= Thoughts and feelings of incapacity, fatigue or weakness related to activities; work or hobbies
2= Loss of interest in activity; hobbies or work—either directly reported by patient, or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities)
3= Decrease in actual time spent in activities or decrease in productivity
4= Stopped working because of present illness

8. RETARDATION: PSYCHOMOTOR
(Slowness of thought and speech; impaired ability to concentrate; decreased motor activity)
0= Normal speech and thought
1= Slight retardation at interview
2= Obvious retardation at interview
3= Interview difficult
4= Complete stupor

9. AGITATION
0= None
1= Fidgetiness
2= Playing with hands, hair, etc.
3= Moving about, can't sit still
4= Hand wringing, nail biting, hair-pulling, biting of lips

10. ANXIETY (PSYCHOLOGICAL)
0= No difficulty
1= Subjective tension and irritability
2= Worrying about minor matters
3= Apprehensive attitude apparent in face or speech
4= Fears expressed without questioning

11. ANXIETY SOMATIC: Physiological concomitants of anxiety, (i.e., effects of autonomic over activity, "butterflies," indigestion, stomach cramps, belching, diarrhea, palpitations, hyperventilation, paresthesia, sweating, flushing, tremor, headache, urinary frequency).Avoid asking about possible medication side effects (i.e., dry mouth, constipation)

0= Absent
1= Mild
2= Moderate
3= Severe
4= Incapacitating

12. SOMATIC SYMPTOMS (GASTROINTESTINAL)
0= None
1= Loss of appetite but eating without encouragement from others. Food intake about normal
2= Difficulty eating without urging from others. Marked reduction of appetite and food intake

13. SOMATIC SYMPTOMS GENERAL
0= None
1= Heaviness in limbs, back or head. Backaches, headache, muscle aches. Loss of energy and fatigability
2= Any clear-cut symptom rates 2

14. GENITAL SYMPTOMS (Symptoms such as: loss of libido; impaired sexual performance; menstrual disturbances)
0= Absent
1= Mild
2= Severe

15. HYPOCHONDRIASIS
0= Not present
1= Self-absorption (bodily)
2= Preoccupation with health
3= Frequent complaints, requests for help, etc.
4= Hypochondriacal delusions

16. LOSS OF WEIGHT
A. When rating by history:
0= No weight loss
1= Probably weight loss associated with present illness
2= Definite (according to patient) weight loss
3= Not assessed

17. INSIGHT
0= Acknowledges being depressed and ill
1= Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
2= Denies being ill at all.

18. DIURNAL VARIATION

A. Note whether symptoms are worse in morning or evening. If NO diurnal variation, mark none

0= No variation

1= Worse in A.M.

2= Worse in P.M.

B. When present, mark the severity of the variation. Mark "None" if NO variation

0= None

1= Mild

2= Severe

19. DEPERSONALIZATION AND DEREALIZATION (Such as: Feelings of unreality; Nihilistic ideas)

0= Absent

1= Mild

2= Moderate

3= Severe

4= Incapacitating

20. PARANOID SYMPTOMS

0= None

1= Suspicious

2= Ideas of reference

3= Delusions of reference and persecution

21. OBSESSIONAL AND COMPULSIVE SYMPTOMS

0= Absent

1= Mild

2= Severe

TOTAL SCORE___

With metabolic syndrome

Sl No	Age	Sex	Religion	Marital status	Education	Occupation	Locality	Diet	WC(cm)	BMI	BP	FBS	PPBS	HDL	TG	FT3	FT4	TSH	Age	Age at onset	Index episode	No.of episodes				current episode	YMRS	HAMD	Alcohol use		
																						Mania	Depression	Mixed	Total				Use	Abuse	Dependence
1	49	M	H	1	2	1	2	2	94	23	120/90	110	140	34	150	4	2	5	49	23	2	4	3	0	7	2	0	14	1	1	2
2	52	M	H	1	2	1	2	2	98	24	120/80	116	142	36	148	5	2	6	52	22	2	4	4	0	8	2	0	15	1	1	2
3	48	M	H	1	2	1	2	2	96	25	126/88	111	141	39	142	4	2	5	48	23	2	3	3	0	6	1	11	0	1	1	2
4	44	M	H	1	2	1	2	2	101	29	128/90	114	142	44	155	4	2	6	44	24	2	3	2	0	5	1	14	0	1	2	1
5	45	M	H	1	2	1	2	2	87	26	130/90	105	144	38	143	4	2	5	45	25	1	2	3	0	5	1	12	0	1	2	1
6	49	M	H	3	2	1	1	2	96	29	134/86	103	136	40	148	4	2	5	49	26	1	3	2	1	6	1	16	0	1	2	2
7	43	M	NH	1	2	1	2	1	99	28	132/88	109	139	41	151	3	1	2	43	21	3	3	1	1	5	2	0	17	1	2	2
8	45	M	H	1	2	1	2	2	100	28	135/86	112	140	39	147	3	1	2	45	27	1	2	4	0	6	1	14	0	1	2	1
9	42	M	H	1	2	1	2	2	97	27	130/90	104	137	33	146	3	1	4	42	25	1	3	2	0	5	2	0	18	1	2	1
10	44	M	H	1	2	1	1	2	99	25	130/90	109	142	34	149	3	1	4	44	21	3	3	2	1	6	1	17	0	1	1	2
11	50	M	NH	1	2	1	2	2	103	29	138/90	115	141	35	151	3	1	4	50	26	1	4	3	0	7	2	0	16	1	1	2
12	30	M	H	1	2	1	2	2	88	23	138/92	112	139	38	155	4	1	2	30	25	1	4	1	0	5	1	11	0	1	2	1
13	46	M	H	1	1	2	1	2	94	23	140/86	119	135	42	149	3	1	1	46	27	1	5	2	1	8	1	14	0	1	2	1
14	49	M	H	3	1	2	2	2	92	22	140/90	107	140	40	150	3	1	1	49	26	1	4	3	0	7	2	0	17	1	2	2
15	47	M	H	1	1	2	2	2	96	24	136/88	108	143	39	154	3	1	2	47	28	1	4	2	0	6	2	0	19	1	2	2
16	45	M	H	1	2	1	1	2	105	30	136/86	107	142	38	157	4	1	2	45	25	1	3	4	0	7	2	0	21	1	2	1

Sl No	Age	Sex	Religion	Marital status	Education	Occupation	Locality	Diet	WC(cm)	BMI	BP	FBS	PPBS	HDL	TG	FT3	FT4	TSH	Age	Age at onset	Index episode	No.of episodes				current episode	YMRS	HAMD	Alcohol use		
																						Mania	Depression	Mixed	Total				Use	Abuse	Dependence
17	45	F	H	1	1	2	2	1	86	28	136/90	111	132	49	145	4	1	3	45	29	1	5	1	0	6	2	0	19	2		
18	51	F	H	1	2	1	2	2	88	29	130/94	112	136	48	146	3	1	3	51	26	1	5	3	0	8	1	18	0	2		
19	30	F	NH	1	2	1	2	2	78	22	136/90	113	137	47	153	3	2	4	30	25	1	3	1	0	4	1	14	0	2		
20	48	F	H	1	1	2	2	2	83	28	130/90	109	140	53	149	4	1	4	48	26	1	1	5	0	6	2	0	20	2		
21	54	F	H	3	1	2	1	2	91	26	135/88	108	142	54	140	4	2	3	54	28	1	4	2	2	8	1	15	0	2		
22	56	F	H	3	2	1	2	2	85	24	130/90	107	143	57	139	3	1	3	56	27	1	1	8	0	9	1	15	0	2		
23	45	F	H	1	2	1	1	2	94	22	138/86	106	132	49	142	3	1	2	45	25	1	4	2	0	6	2	0	19	2		
24	44	F	H	1	2	1	2	2	82	25	140/90	114	139	45	146	3	2	1	44	26	1	5	2	0	7	2	0	21	2		
25	53	F	H	1	1	2	2	2	89	27	135/90	113	142	47	150	3	1	1	53	25	1	2	6	0	8	2	0	23	2		
26	43	F	H	1	2	1	2	2	85	24	135/88	112	147	48	143	4	1	6	43	27	1	5	1	0	6	1	17	0	2		
27	45	F	NH	1	1	2	2	2	88	23	132/90	111	138	46	141	4	1	6	45	29	1	3	2	0	5	1	18	0	2		
28	51	F	H	1	1	2	2	2	90	24	130/92	99	139	45	153	5	1	5	51	23	2	5	2	0	7	2	0	16	2		
29	57	F	H	1	1	2	2	2	95	27	136/92	96	146	49	151	4	1	5	57	24	2	5	3	0	8	2	0	14	2		
30	53	F	H	1	1	2	2	2	97	28	130/90	97	141	48	152	4	1	6	53	23	2	5	2	0	7	2	0	17	2		

Bipolar Disorder Without metabolic syndrome

Sl.NO	Sex	Age	Religion	Marital status	Education	Occupation	Locality	Diet	WC	BMI	BP	FBS	PPBS	HDL	TG	T3	T4	TSH	Age	Age at onset	Index episode	No.of episodes				Current episode	YMRS	HAMD	Alcohol use		
																						Mania	Depression	Mixed	Total				Use	Abuse	Dependence
1	M	15	NH	2	2	2	2	2	80	22	110/70	68	120	49	141	2.8	0.8	0.7	18	16	1	2	0	0	2	1	18	0	1	2	2
2	M	21	H	2	1	1	2	2	82	21	114/80	79	134	44	132	2.6	1.5	1.7	24	20	2	2	1	0	3	1	20	0	1	2	2
3	M	23	H	2	1	1	2	2	84	23	122/76	82	127	56	145	3.2	1.7	2.3	25	21	2	2	1	0	3	1	19	0	1	1	1
4	M	26	H	2	1	1	2	2	79	18	120/70	90	139	50	139	3.6	0.9	2.9	26	21	1	3	1	0	4	2	0	13	1	1	1
5	M	28	H	2	1	1	2	2	86	20	120/76	94	128	44	136	2.9	1.1	1.9	30	28	1	2	0	0	2	1	21	0	1	2	2
6	M	29	H	1	2	1	2	2	81	19	110/82	88	131	48	138	2.8	1.2	3.1	29	26	1	3	1	0	4	1	20	0	1	1	2
7	M	31	H	1	2	1	2	2	84	22	110/80	76	111	51	129	3.9	1.4	2.3	31	27	1	2	2	0	4	1	18	0	1	1	2
8	M	35	H	1	2	1	2	2	80	20	120/70	79	119	49	152	3.5	0.8	5.2	35	25	1	2	2	1	5	1	17	0	1	1	2
9	M	36	H	1	1	1	2	2	85	22	126/70	90	122	45	126	3.8	1.1	1.6	36	24	1	3	2	0	5	2	0	14	1	1	1
10	M	38	H	1	2	1	2	2	91	29	120/80	80	127	50	156	2.6	1.2	1.9	38	25	1	3	1	2	6	2	0	13	1	2	2
11	M	38	H	1	1	1	2	2	87	22	110/82	94	120	49	158	2.9	1.5	1.7	38	26	1	4	1	0	5	1	21	0	1	1	2
12	M	39	H	1	2	1	2	2	86	22	120/90	98	124	40	140	4.1	0.9	5.8	39	23	1	3	1	0	4	1	18	0	2	2	2
13	M	35	H	1	2	1	2	2	91	26	110/70	88	112	45	147	3.4	0.9	2.8	35	26	1	4	2	0	6	1	18	0	2	2	2
14	M	34	H	1	2	1	2	1	95	24	110/70	90	111	52	122	3.5	1.2	3.6	34	26	1	4	1	0	5	2	0	12	2	2	2
15	M	46	H	1	2	1	1	2	93	31	114/78	78	130	47	145	2.6	1.1	3.5	46	28	1	5	1	0	6	2	0	15	2	2	2

Sl.NO	Sex	Age	Religion	Marital status	Education	Occupation	Locality	Diet	WC	BMI	BP	FBS	PPBS	HDL	TG	T3	T4	TSH	Age	Age at onset	Index episode	No.of episodes				Current episode	YMRS	HAMD	Alcohol use		
																						Mania	Depression	Mixed	Total				Use	Abuse	Dependence
16	M	57	H	1	1	1	1	1	80	21	130/90	69	131	39	123	2.9	1.4	3.1	57	27	1	4	3	0	7	2	0	11	2	2	2
17	F	18	NH	2	1	1	2	2	68	19	130/80	82	134	51	125	2.8	1.3	1.9	29	25	1	3	0	0	3	1	20	0	2	2	2
18	F	20	H	2	1	1	2	2	72	18	120/90	80	125	55	129	3.1	1.5	1.6	28	20	3	3	0	2	5	1	21	0	2	2	2
19	F	21	H	2	1	1	2	2	71	20	110/74	90	136	53	137	3.5	1.1	2.4	29	26	1	2	0	0	2	1	19	0	2	2	2
20	F	27	H	1	2	1	2	2	69	19	124/80	77	115	52	136	3.9	1.6	2.7	28	26	1	2	0	0	2	1	18	0	2	2	2
21	F	29	H	1	2	1	2	2	73	22	122/78	87	117	54	142	4.2	0.8	5.8	29	25	1	3	0	0	3	1	17	0	2	2	2
22	F	32	H	1	2	2	2	2	77	21	110/74	88	121	54	156	3.2	1.5	1.6	32	28	1	2	0	0	2	1	24	0	2	2	2
23	F	32	H	1	2	1	2	2	78	19	130/88	94	122	56	128	2.7	1.3	3.1	32	26	1	2	0	1	3	1	26	0	2	2	2
24	F	33	H	1	1	2	2	2	76	22	120/80	96	119	51	130	4.2	0.9	5.4	33	25	1	3	1	0	4	1	28	0	2	2	2
25	F	35	H	1	1	2	1	2	87	29	110/70	80	122	52	125	2.8	1.4	3.2	35	28	1	3	0	0	3	1	19	0	2	2	2
26	F	39	H	1	2	2	1	2	79	21	126/88	80	130	50	140	3.1	0.8	5.7	39	27	1	3	2	0	5	2	0	14	2	2	2
27	F	40	H	1	1	2	2	2	86	30	120/80	86	130	56	130	3.3	1.2	1.9	40	27	1	3	1	0	4	1	23	0	2	2	2
28	F	40	NH	1	1	2	2	2	81	23	120/70	90	126	57	115	3.8	1.1	2.3	40	26	1	1	4	0	5	2	0	14	2	2	2
29	F	42	H	1	1	2	1	2	82	24	110/80	68	100	51	126	4.1	0.9	5.9	42	28	1	2	2	0	4	2	0	15	2	2	2
30	F	44	H	1	1	2	1	1	85	25	100/80	84	114	60	133	3.9	0.8	2.6	44	28	1	2	4	0	6	2	0	12	2	2	2
31	F	49	H	1	1	2	1	1	88	29	120/86	88	100	56	154	2.7	0.9	1.8	49	23	2	2	4	0	6	2	0	13	2	2	2