

Metabolic syndrome in Tunisian bipolar I patients

*Ezzaher A^{1,2}, Haj Mouhamed D¹, Mechri A², Neffati, F¹, Douki W¹, Gaha, L¹, Najjar MF¹,

1. University Hospital of Monastir, Laboratory of Biochemistry-Toxicology

2. Research Laboratory "Vulnerability to Psychotic disorders LR 05 ES 10", Department of Psychiatry, University Hospital of Monastir

Abstract

Background: The metabolic syndrome is a growing global public health problem which is frequently associated with psychiatric illness.

Objectives: To evaluate the prevalence of metabolic syndrome and to study its profile in Tunisian bipolar I patients.

Methods: Our study included 130 patients with bipolar I disorder diagnosed according to the DSM-IV and assessed for metabolic syndrome according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III modified criteria. The mean age was 37.9 ± 12.1 years, 45 were women (mean age 37.5 ± 13.4 years) and 85 were men (mean age 38.1 ± 11.4 years).

Results: The prevalence of metabolic syndrome was 26.1%. The highest prevalence of this syndrome was obtained by association between obesity, low c-HDL and hypertriglyceridemia (44.1%). In the total sample, 59.2% met the criteria for low c-HDL, 53.1% for hypertriglyceridemia, 33.8% for obesity, 16.1% for high fasting glucose and 5.4% for hypertension. Gender, age, illness episode and treatment were not significantly associated with metabolic syndrome, while patients under lithium had higher prevalence of metabolic syndrome than those under valproic acid, carbamazepine or antipsychotics. Patients with metabolic syndrome had significant higher levels of HOMA-IR and uric acid than metabolic syndrome free patients ($p < 0.001$).

Conclusions: Bipolar patients have high prevalence of metabolic syndrome which is associated with insulin resistance and an increase of uric acid values that raise the risk of cardiovascular disease.

Key words: bipolar disorder, metabolic syndrome, uric acid, insulin resistance.

African Health Sciences 2011; 11(3): 414 - 420

Introduction

Bipolar disorders are common conditions, affecting approximately 3.5% of the population, and are characterized by recurrent episodes of depression and mood elevation¹. It is a chronic disease that is associated with a potentially devastating impact on the patients' wellbeing and social, occupational, and general functioning². The disorder ranks as the sixth leading cause of disability in the world, with an economic burden that in the US alone was estimated more than a decade ago at \$7 billion in direct medical costs and \$38 billion (1991 values) in indirect costs³. Patients with bipolar disorder are known to suffer a considerable number of associated pathologies that

may manifest at earlier ages and with higher frequency than in the general population⁴. The most recent studies have explored cardiovascular risk and the association with metabolic and endocrine disorders fundamentally, obesity and metabolic syndrome which are clearly associated with the development of cardiovascular disease⁵. The metabolic syndrome is composed of a number of risk factors including insulin resistance, abdominal obesity, dyslipidemia, and hypertension and is associated with an increase in morbidity and mortality⁶.

Various studies conducted in bipolar patients report prevalence of metabolic syndrome rates from 16-25% in European subjects^{7, 8} to 30-49% in U.S. subjects^{6, 9}. Although, data in African area remain scarce, some studies performed in the African-American patients reported prevalence rates from 22.5% to 44%^{6, 10}.

This study aims to evaluate the prevalence of metabolic syndrome and to study its profile in 130 Tunisian bipolar I patients.

*Correspondence author

Asma Ezzaher

University Hospital of Monastir

Laboratory of Biochemistry-Toxicology

Research Laboratory Vulnerability to Psychotic disorders LR 05 ES 10

Department of Psychiatry, University Hospital of Monastir, Tunisia

Email: ezzaherasma@yahoo.fr

Methods

Patients

This study was approved by the local ethical committee of Monastir University Hospital, and all subjects were of Tunisian origin. The sample included 130 bipolar I patients from the psychiatry department of the Teaching Hospital of Monastir with depressive (D=21), manic (M=36) or euthymic (E=73) episode.

Patients included in the study were required to receive medications (mood stabilizers: valproic acid, lithium and carbamazepine, and classical or atypical antipsychotics such as risperidone or olanzapine) for at least three months.

The mean age was 37.9 ± 12.1 years, with 45 women (37.5 ± 13.4 years) and 85 men (38.1 ± 11.4 years). Consensus on the diagnosis, according to the diagnostic and Statistical manual of Mental disorders, fourth edition (DSM-IV) criteria¹¹, was made by psychiatrists. The exclusion criteria were age (<18 years), other psychiatric illnesses, epilepsy or mental retardation.

All subjects were questioned about their age, gender, previous treatments and cigarette and alcohol consumption habits. The clinical and sociodemographic characteristics are shown in Table 1.

Table 1: Sociodemographic and therapeutic characteristics of bipolar I disorder

Characteristics	Values
Gender , male/female (ratio)	85/45 (1.89)
Age , years \pm SD	37.9 ± 12.1
BMI , kg/m ² \pm SD	27.13 ± 4.57
Cigarette smoking	
Yes	68(52.3%)
No	62(47.7%)
Alcoholic consumption	
Yes	17(13%)
No	113(87%)
Illness episode	
Depressive (D)	21 (16%)
Euthymic (E)	73 (56%)
Manic (M)	36 (28%)
Treatment	
Mood stabilizers	92(70.8%)
Valproic acid	64(69.5%)
Lithium	12(13%)
Carbamazepine	10(11%)
Lithim and valproic acid	6(6.5%)
Antipsychotics	38(29.2%)

All values are n (%) unless otherwise stated.

BMI = body mass index.

Samples

After a 12 hour overnight fasting, venous blood for each patient was drawn in tubes containing lithium heparinate and immediately centrifuged. The plasma samples were stored at -20°C until the biochemical analysis.

Biochemical analysis

Metabolic syndrome (MS) was defined according to the National Cholesterol Education program (NCEP) Adult Treatment panel (ATP) III modified criteria and required fulfillment of at least three of the following five components: body mass index (BMI) ≥ 28.8 kg/m², triglycerides ≥ 1.7 mmol/L, high-density lipoprotein cholesterol (c-HDL) < 1.1 mmol/L (men) and < 0.9 mmol/L (women), blood pressure ≥ 130 D 85 mmHg, and fasting glucose (≥ 6.1 mmol)¹².

Concentrations of triglycerides, c-HDL, fasting glucose and uric acid were determined by enzymatic methods using Konelab 30 equipment (Thermo Electron Corporation, Ruukintie, Finland). Insulin was determined using chemiluminescence (Elecsys 2010™ Roche diagnostics).

Data measures

Insulin resistance (IR) was estimated using the Homeostasis model of assessment equation: HOMA-IR = [fasting insulin (mU/L) \times fasting glucose (mmol/L)] / 22.5. The IR was defined as the upper quartile of HOMA-IR. Values above 2.5 were taken as abnormal and reflect insulin resistance¹³.

Bipolar patients with diabetes (n = 21) were excluded in the HOMA-IR analysis.

The BMI was calculated as weight (kg) divided by height (m²). Obesity was defined when BMI was ≥ 28.5 kg/m²¹².

Statistical analyses

Statistical analyses were performed using SPSS v. 17.0 (SPSS, Chicago, IL, USA). Quantitative variables were presented as mean \pm SD and comparisons were performed using the Student's t test. Qualitative variable comparisons were performed using the chi square test and Fisher's exact test (when cells with n < 5). The statistical significance level was set at $p < 0.05$.

Results

In our study, the prevalence of metabolic syndrome in bipolar I patients was 26.1% (table 2). The highest

prevalence of this syndrome was obtained by the association between obesity, low c-HDL and hypertriglyceridemia (44.1 %) (table 2).

Table 2: Prevalence of metabolic syndrome (modified National Cholesterol Education Program Adult Treatment Panel III criteria) and its profile in bipolar I patients

	N	%
Total of the association of 5 criteria	2	5.9
Total of the association of 4 criteria	3	8.8
Total of the association of 3 criteria	29	85.3
At least three or more criteria	34	100

In the total sample, the prevalence of individual diagnostic components was as follows: 59.2% for low c-HDL, 53.1% for hypertriglyceridemia, 33.8% for obesity, 16.1% for high fasting glucose and 5.4% for hypertension (Table 3).

Table 3: Prevalence of the components of metabolic syndrome (modified National Cholesterol Education Program Adult Treatment Panel III criteria) in the total sample (N= 130)

Criteria	N (%)
cHDL < 1.1 mmol/L (men) and < 0.9 (women)	77(59.2)
TG ≥ 1.7 mmol/L	69(53.1)
BMI ≥ 28.8 kg/m ²	44 (33.8)
Fasting blood glucose ≥ 6.1 mmol/L	21 (16.1)
Blood pressure ≥ 130/85 mm Hg	7(5.4)
At least three or more criteria	34 (26.1)

Table 4: Characteristics of patients with or without metabolic syndrome (modified National Cholesterol Education Program Adult Treatment Panel III criteria)

Variables	With MS	Without MS	p values
	[N= 34 (26.1%)]	[N= 96 (73.9%)]	
	N (%)	N (%)	
Gender			
Men	21 (24.7)	64 (75.3)	0.60
Women	13 (28.9)	32 (71.1)	
Cigarette smoking			
Yes	16 (23.5)	52 (76.5)	0.47
No	18 (29.1)	44 (70.9)	
Alcoholic consumption			
Yes	6 (35.3)	11 (64.7)	0.35
No	28 (24.8)	85 (75.2)	
Illness episode			
Depressive (D)	4 (19)	17 (81)	0.65 ^a
Euthymic (E)	19 (26)	54 (74)	
Manic (M)	11 (30.5)	25 (69.5)	

We found that gender was not associated with metabolic syndrome, 24.7% in men and 28.9% in women. As to age, we found that patients with metabolic syndrome were older than metabolic syndrome free patients (40.4 ± 8.8 years *Vs* 37.0 ± 12.7 years), but this difference was not significant. Cigarette smoking and alcoholic consumption were not significantly associated with metabolic syndrome; however, we showed that approximately a quarter (23.5%) of smoker patients and a third (35.3%) of alcoholic consumer patients had metabolic syndrome (Table 4).

Our present data showed that there is no difference in metabolic syndrome prevalence between patients receiving antipsychotic and mood stabilizers treatment. However, we noted that patients treated with lithium had the highest prevalence of metabolic syndrome.

Our study failed to show any significant association between metabolic syndrome and illness episode, whereas, manic patients had the highest prevalence of this disorder (30.5%)

Patients with metabolic syndrome had significantly higher levels of uric acid (p < 0.001) than metabolic syndrome free patients.

Concerning HOMA-IR analysis, after diabetic patients exclusion (n = 21), we noted that patients with metabolic syndrome had significantly higher levels of HOMA-IR (p < 0.001) than metabolic syndrome free patients.

Variables	With MS	Without MS	p values
	[N= 34 (26.1%)]	[N= 96 (73.9%)]	
	N (%)	N (%)	
Treatment			
Antipsychotics	10 (26.3)	28 (73.7)	0.95 ^a
Mood stabilizers	24 (26.1)	68 (74.9)	
Lithium	4 (33.3)	8 (66.7)	
Valproic acid	17 (26.6)	47 (73.4)	
Carbamazepine	2 (20)	8 (80)	
Lithium/valproic acid	1 (16.7)	5 (83.3)	
	Mean ± SD	Mean ± SD	P
Age (years)	40.4 ± 8.8	37.0 ± 12.7	0.11
HOMA-IR	6.0 ± 4.3*	2.4 ± 1.7**	< 0.001
Uric acid (μmol/L)	335 ± 117	272 ± 92	< 0.001

* n = 23 (11 diabetic patients were excluded)

** n = 86 (10 diabetic patients were excluded)

^a Statistical analysis was conducted using Fisher's exact test.

Discussion

To our knowledge, this is the first study to examine the prevalence and correlates of metabolic syndrome in Tunisian patients with bipolar I disorder. Using the ATP-III definition, we found that the prevalence of metabolic syndrome was 26.1% among patients, (24.7% in men and 28.9% in women). These prevalences were definitely higher than those reported in the Tunisian general population (13% in men and 18% in women) using a previous criteria¹⁴.

Compared with others studies, the prevalence of metabolic syndrome in our patients is between that in Spanish patients (22.4%)¹⁵, Italian patients (25.3%)⁸ and US patients (30%)⁹. The highest prevalence of metabolic syndrome was obtained by association between obesity, low c-HDL and hypertriglyceridemia, confirming the high risk of dyslipidemia and obesity in bipolar I patients¹⁶. There is a need for psycho educational programmes including healthier eating habits and lifestyle advice for patients with bipolar disorder. Furthermore, effective programmes aimed at early detection and adequate treatment by the psychiatric team should be considered. Implementation of programmes that emphasise lifestyle modification to reduce weight in overweight/obese patients can positively influence many components of metabolic syndrome¹⁵.

Moreover, when analyzing the prevalence of the single components of metabolic syndrome in the total sample, we found that lipid disorders (low c-HDL and hypertriglyceridemia) and obesity were the most common abnormalities. This is in line with results reported by Garcia-Portilla et al¹⁵. We

found that 59.2% of bipolar patients met the criteria of low c-HDL, 53.1% of hypertriglyceridemia and 16.1% of high fasting glucose, which are higher than in Italian⁸ and in US patients⁹ (23%, 48% and 11%; 36.1%, 38.2% and 8% respectively). However, the prevalence of obesity (33.8%) and hypertension (5.4%) in our patients were lower than in Italian patients (50% and 40% respectively)⁸ and US patients (49% and 39% respectively)⁹. These differences could be due to ethnicity and eating habits.

Concerning socio-demographic characteristics, there was no significant difference in the prevalence of metabolic syndrome among gender and age. This is in line with results reported by Yumru et al¹⁷.

Cigarette smoking was not significantly associated with metabolic syndrome, but we showed that approximately a quarter of smoker patients had metabolic syndrome. There are several possible explanations for the association between smoking and metabolic syndrome in former smokers. First¹⁸, mechanisms for these long lasting effects of smoking on insulin resistance may include vascular changes that lead to decreased glucose uptake by skeletal muscle. Second^{19,20}, smoking increases the circulating white blood cell count, a marker of inflammation, in subjects undergoing general health screening. It is possible that proinflammatory cytokines, such as tumor necrosis factor- α may explain the association between smoking, increased white blood cell count, and metabolic syndrome. Third^{21,22}, both current and former smoking are negatively associated with plasma levels of adiponectin. Decreased adiponectin

is thought to play a major role in the development of insulin resistance; thus, it may be an underlying mechanism of metabolic syndrome in smokers.

We found that alcoholic consumption is not significantly associated with metabolic syndrome probably because of the small size of alcoholic consumer patients ($n = 17$). However, we showed that approximately a third of alcoholic consumer patients had metabolic syndrome. Some studies have shown positive association, whereas others have observed a negative association or no relation at all²³. This irregularity in results could be related to the complex mechanistic relation between alcohol consumption and each component of metabolic syndrome. While mild to moderate alcohol consumption has a favourable influence on lipids metabolism, abdominal obesity and glucose regulation, excessive alcohol consumption causes hypertension and hypertriglyceridemia constituting alcohol-related metabolic syndrome²³.

We noted that there was no significant change in the prevalence of metabolic syndrome in relation to illness episode; however, manic patients had the highest prevalence. This may explain the high risk of cardiovascular disease in manic patients compared with depressive one²⁴. Additionally, Angst et al²⁵ showed that individuals with bipolar I disorder are at greater risk for cardiovascular mortality than individuals with bipolar II disorder. However, the difference in cardiovascular mortality between the two bipolar subtypes reflects the manic symptom burden, which predicts cardiovascular mortality independently of diagnosis and cardiovascular risk factors at intake. The results suggest that mania, either directly (through factors intrinsic to illness) or indirectly (through other mediators or associated variables), may itself influence cardiovascular disease.

Our study failed to show any significant association between metabolic syndrome and treatment. However, we noted that patients treated with lithium had the highest prevalence of metabolic syndrome. The increased risk to develop metabolic syndrome during treatment with lithium is in part related to its propensity to induce weight gain. According to Casey²⁶, lithium has been shown to stimulate appetite and increase calorie intake through different mechanisms.

The HOMA-IR is significantly higher ($p < 0.001$) in patients with metabolic syndrome than others. This increase in HOMA-IR values reflects an insulin resistance and is associated with two to three fold increases in cardiovascular disease independent of classical risk factors²⁷. In addition, uric acid levels

were significantly higher ($p < 0.001$) in patients with metabolic syndrome. According to Vuorinen-Markkola et al²⁸, hyperuricemia forms another consistent feature of the metabolic syndrome which led to the suggestion of uric acid being a new component of the syndrome.

In addition, Chien et al²⁹ reported that metabolic syndrome induces high oxidative stress and the accompanying hyperuricemia worsens this stress. Furthermore, uric acid stimulates vascular smooth muscle proliferation, induces endothelial dysfunction, decreases endothelial nitric oxide production, and consequently, makes peripheral tissue resistant to insulin effects and results in endothelial dysfunction²⁹. High levels of uric acid are associated with increased renal glomerular pressure and sodium reabsorption, enhanced by high insulin concentrations²³. In addition, hyperuricemia was associated with insulin resistance markers, including triglycerides, microalbuminuria and impaired glucose tolerance. These disturbances contribute to increase cardiovascular risk²⁹. This insulin-resistance causes steatosis, which is associated with hyper secretion of hepatic enzymes³⁰.

Several methodological limitations should be considered when interpreting these findings. First, a larger sample size of groups would be beneficial. Second, our work is a cross-sectional study that does not permit follow-up of biological parameters. Finally, the sample of bipolar patients may not be representative of more heterogeneous populations.

Tunisian bipolar I patients have a higher prevalence of metabolic syndrome compared with the general population. The highest prevalence of this syndrome was obtained by association between obesity, low c-HDL and hypertriglyceridemia. Age, gender, illness episode, and treatment were not significantly associated with metabolic syndrome; but insulin resistance and uric acid were significantly associated with this syndrome. The combination effects of these parameters on metabolic syndrome results in high cardiovascular risk.

Conclusion

Bipolar patients require specific care, particularly for lipid profile and weight. The effectiveness of this care will be evaluated during follow-up period. .

Acknowledgements

The authors thank the patients and control subjects for their assistance in this study.

AE conceived the study, gathered and managed the data, carried out the immunoassays, performed the literature search and statistical analysis and wrote the paper. DHM participated in the literature search, the management of the data, statistical analysis and writing of the paper. AM contributed to the clinical and rating evaluations during the follow-up periods, participated in the statistical analysis and in correction of the final manuscript. FN participated in carrying out the immunoassays. WD participated in designing the study, analysing the data, writing the paper and in correction of the final manuscript. LG contributed to the clinical and rating evaluations during the follow-up periods. MFN participated in designing the study, analysing the data, writing the paper and in correction of the final manuscript. All authors read and approved the final manuscript.

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