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Cardiovascular Risk in Tunisian Patients with Bipolar I Disorder

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1. Introduction

Bipolar disorder (previously also labeled manic-depressive illness) is typically referred to as an episodic, yet lifelong and clinically severe affective (or mood) disorder, affecting approximately 3.5% of the population (Marmol, 2008; Simon, 2003; Wittchen et al., 2003; Woods, 2000). The term bipolar disorder, however, encompasses several phenotypes of mood disorders, i.e. mania, hypomania or cyclothymia that may present with a puzzling variety of other symptoms and disorders. According to the Fourth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Association, 2004), the diagnostic classificatory system used in most epidemiological studies, bipolar disorder is defined by a set of specific symptom criteria. Bipolar type I requires the presence or the history of at least one manic or mixed episode. Although, typically, patients with a manic episode also experience major depressive episodes, bipolar disorder can be diagnosed even if only one manic episode and no past major depressive episodes are present. Bipolar disorder type II differs from type I only by presence of hypomanic but no manic episodes. Hypomanic episodes differ from mania by a shorter duration (at least 4 days instead of 1 week), and less severe impairment (not severe enough to cause marked impairment in social or occupational functioning, psychiatric hospitalization, or psychotic features). The DSM-IV also includes "cyclothymia" as a bipolar spectrum disorder with hypomanic as well as depressive episodes that do not meet criteria for major depression (American Psychiatric Association, 2004).

Bipolar disorder is a chronic disease that is associated with a potentially devastating impact on patients' wellbeing and social, occupational, and general functioning (Revicki et al., 2005). The disorder ranks as the sixth leading cause of disability in the world, with an economic burden that in the US alone that was estimated more than a decade ago at $7 billion in direct medical costs and $38 billion (1991 values) in indirect costs (Wyatt et al., 1991).

A number of reviews and studies have shown that people with severe mental illness, including bipolar disorder, have an excess mortality, being two or three times as high as that

in the general population. This mortality gap, which translates to a 13-30 year shortened life expectancy in severe mental illness patients, has widened in recent decades, even in countries where the quality of the health care system is generally acknowledged to be good. About 60% of this excess mortality is due to physical illness especially cardiovascular disease. Additionally, several studies have found that after suicide and accidents, cardiovascular and all vascular diseases are the main leading causes of death in these patients (De Hert et al., 2011; Garcia-Portilla et al., 2009).

Patients with bipolar disorder, especially type I, are known to suffer a considerable number of associated pathologies that may manifest at earlier ages and with higher frequency than in the general population. 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 disease (Angst et al., 2002; Sicras et al., 2008).

Cardiovascular disease, i.e. coronary heart disease, stroke, and peripheral vascular disease, are potentially preventable diseases. Thanks to epidemiological, experimental and clinical studies, the primary determinants of cardiovascular disease have been identified, as well as the efficacy of specific interventions. The prevalence of cardiovascular disease is increasing in less urbanized, developed populations across the world, as their lifestyles change to a so called "western style", with increasing consumption of dietary saturated fat, cholesterol and salt, cigarette smoking, decreased physical activity and the rise in cardiovascular risk factors including obesity and diabetes. Other known factors that contribute to cardiovascular disease risk are stress and high alcohol intake. Among all these factors, hypercholesterolemia is the leading cause of death from cardiovascular disease. As a result, public health agencies have attempted to reduce the prevalence of hypercholesterolemia through screening and by increasing public awareness and strategies for reducing it (Muntoni et al., 2009).

The exact mechanisms increasing the incidence of cardiovascular risk in bipolar patients remain to be clarified, but they possibly include industrialisation, stress, lack of exercise, dietary lipids (that is, omega-3 fatty acid deficiency) and increasing incidence of smoking and alcohol consumption and other factors (Ezzaher et al., 2010).

This study aims to investigate the principal factors predisposing to the cardiovascular risk in Tunisian bipolar I patients (cigarette smoking, hypertension, diabetes, obesity, lipid profile, hyperhomocysteinemia and metabolic syndrome) and to determine the association between these factors and the clinical and therapeutic characteristics of bipolar I disorder.

2. Patients and methods

2.1 Subjects

This study was approved by the local ethical committee and all subjects were of Tunisian origin. Our samples included 130 patients with bipolar I disorder (37.9 ± 12.1 years) from the psychiatry department of the University Hospital of Monastir, Tunisia, 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) criteria (American Psychiatric Association, 2004), was made by psychiatrists. The exclusion criteria were age < 18 years, other psychiatric illnesses, epilepsy or mental retardation. The control group consisted of 175 volunteer subjects without psychiatric pathology. The mean age was 40.1 ± 14.0 years, and there were 73 women (42.0 ± 14.4 years) and 102 men (38.8 ± 13.6

years). All subjects were questioned about their age, gender, previous treatments and cigarette and alcohol consumption habits.
The clinical and socio-demographic characteristics are shown in table 1. Differences between patients and controls for body mass index (BMI) ($p < 0.001$) and smoking status ($p = 0.025$) were noted. Therefore, these variables were considered as potential confounder factors for this analysis.

	Patients (n = 130)		**Controls (n = 175)**		**p**
Gender: Men/Women (ratio)	85/45 (1.89)		102/73 (1.39)		0.143
Age (years) (mean ± SD)	37.9 ± 12.1		40.1 ± 14.0		0.840
BMI (kg/m²) (M ± ET)	27.1 ± 4.6		25.3 ± 4.1		**< 0.001**
	Nombre	**%**	**Nombre**	**%**	**p**
BMI (kg/m²)					
< 25	47	36.2	89	50.9	**< 0.001**
[25-30[	40	30.7	72	41.1	
≥ 30	43	33.1	14	8	
Cigarette smoking					
Yes	68	52.3	69	39.4	**0.025**
No	62	47.7	106	60.6	
Alcoholic beverages					
Yes	17	13.1	12	6.9	0.067
No	113	86,9	163	93.1	
Illness episode					
Depressive	21	16.2	-	-	-
Euthymic	73	56.1	-	-	-
Manic	36	27.7	-	-	-
Treatment					
Valproic acid	64	49.3	-	-	-
Lithium	12	9.2	-	-	-
Carbamazepine	10	7.7	-	-	-
Valproic acid and lithium	6	4.6	-	-	-
Antipsychotics	38	29.2	-	-	-

Antipsychotics: Haloperidol, Risperidone, Chlorpromazine, Olanzapine; BMI: body mass index

Table 1. Sociodemographic and therapeutic characteristics of studied population.

2.2 Samples

After a 12 h 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.

2.3 Biochemical analysis

The methods of dosage and the normal values of the different biological parameters are shown in table 2.

Parameters	Assay	Automates	Normal values
Cholesterol	Enzymatic	Konelab 30 equipment (Thermo Electron Corporation, Ruukintie, Finland)	< 5.17 mmol/L
Triglycerides			< 1.7 mmol/L
c-HDL			Men: ≥ 1.1 mmol/L Women: ≥ 0.9 mmol/L
c-LDL			< 3.4 mmol/L
ApoA1	Immunoturbidimetry		1.2- 1.6 g/L
ApoB			0.7-1.3 g/L
Lp(a)			< 200 mg/L
Uric acid	Enzymatic		Men: 210-420 µmol/L Women: 150-360 µmol/L
Homocysteine	Fluorescence polarization (FPIA)	AxSYM® (Abbott Laboratories, Abbott Park, IL 60064, Barcelaneta, Puerto Rico)	< 15 µmol/L
Vitamin B12	Electrochemiluminescence	Elecsys 2010™ (Roche Diagnostics, Indianapolis, IN, USA)	≥ 187ng/L
Folate			≥ 3.7 µg/L
Insulin			< 17µU/mL

Table 2. Methods of dosage of the studied parameters.

2.4 Clinical evaluation

Body mass index (BMI) was calculated as weight (kg) divided by height (m^2). Obesity was defined when BMI ≥ 30 kg/m^2 and overweight when BMI ≥ 25 kg/m^2 (World Health Organization, 1997).

2.5 Criteria for metabolic syndrome

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) ≥ 28.5 kg/m^2, triglycerides ≥ 1.7 mmol/L, high-density lipoprotein cholesterol (c-HDL) < 1.1 mmol/L (in men) and < 0.9 mmol/L (in women), blood pressure ≥ 130 /85 mmHg and fasting glucose (≥ 6.1 mmol/L) (National Cholesterol Education Program, 2002).

2.6 HOMA-IR determination

Insulin resistance (IR) was estimated using the Homeostasis Model of Assessment equation: HOMA-IR = [fasting insulin (mU/L) × fasting glucose (mmol/L)]/22.5. IR was defined as the upper quartile of HOMA-IR. Values above 2.5 were taken as abnormal and reflect insulin resistance (Ozdemir et al., 2007). Bipolar patients with diabetes (n = 21) were excluded in the HOMA-IR analysis.

2.7 Statistical analysis

Statistical analyses were performed using SPSS 17.0 (SPSS, Chicago, IL, USA). Quantitative variables were presented as mean ± SD and comparisons were performed using the Student's t test. Qualitative variable comparisons were performed using the Chi-squared test (χ^2) and Fisher's exact test (when n < 5). Comparisons between patients and controls in biological parameters were performed using analysis of variance (ANOVA) after adjustment for potential confounder factors. Odd ratios (ORs) and their 95% confidence interval (CI) were calculated and adjusted for potential confounder factors by binary logistic regression. The statistical significance level was set at $p < 0.05$. All variables with a p value < 0.25 between the two studied groups (patients and controls) were considered as potential confounder factors for this analysis.

3. Results

Table 3 shows the comparisons of biological variables between bipolar I patients and controls.

Biological variables	**Patients (n = 130)**	**Controls (n = 175)**	**p**	**p***
Triglycerides (mmol/L)	1.95 ± 1.55	1.23 ± 0.81	**< 0.001**	**< 0.001**
Cholesterol (mmol/L)	4.42 ± 0.99	4.37 ± 1.26	0.707	0.856
c-LDL (mmol/L)	2.14 ± 1.10	2.37 ± 1.38	0.118	0.047
c-HDL (mmol/L)				
Men (85/102)	1.04 ± 0.37	0.98 ± 0.29	0.192	0.017
Women (45/73)	1.17 ± 0.36	1.21 ± 0.48	0.542	0.702
ApoA1 (g/L)	1.20 ± 0.23	1.40 ± 0.67	**< 0.001**	**0.028**
ApoB (g/L)	0.82 ± 0.28	0.83 ± 0.24	0.784	0.777
ApoB/Apo A1	0.71 ± 0.26	0.65 ± 0.25	0.086	0.314
Lp(a) (mg/L)	243 ± 223	87 ± 129	**< 0.001**	**< 0.001**
Homocysteine (µmol/L)	15.8 ± 8.9	11.5 ± 5.0	**< 0.001**	**< 0.001**
Vitamin B12 (ng/L)	356 ± 198	360 ± 190	0.837	0.819
Folate (µg/L)	3.3 ± 0.9	5.1 ± 2.8	**< 0.001**	**<0.001**
Uric acid (µmol/L)				
Men (85/102)	311 ± 99	250 ± 107	**0.001**	**0.005**
Women (45/73)	246 ± 97	197 ± 73	**0.012**	0.408

* Lipid profile parameters, folatemia, vitamin B12 and uric acid were adjusted for gender, BMI, cigarette smoking, alcoholic beverages, diabetes and hypertension

*Hcys was adjusted for gender, BMI, cigarette smoking, alcoholic beverages, diabetes, hypertension, folatemia and vitamin B12

Table 3. Comparisons of biological variables between bipolar I patients and controls.

Compared with controls, patients had significantly higher triglycerides (1.95 ± 1.55 *Vs* 1.23 ± 0.81 mmol/L; p < 0.001), Lp(a) (243 ± 223 *Vs* 87 ± 129 mg/L; p < 0.001), homocysteine levels (15.8 ± 8.9 *Vs* 11.5 ± 5.0 µmol/L; p < 0.001) and uric acid (311 ± 99 *Vs* 250 ± 107 µmol/L; p = 0.001 in men; 246 ± 97 *Vs* 197 ± 73 µmol/L; p = 0.012 in women), and significantly lower ApoA1 (1.20 ± 0.23 *Vs* 1.40 ± 0.67 g/L; p < 0.001) and folate (3.3 ± 0.9 *Vs* 5.1 ± 2.8 µg/L; p < 0.001) levels. After adjustment for potential confounder factors, these differences remained significant for all of these parameters except for uric acid which is remained significantly higher only for men (table 3).

Table 4 reports the association between bipolar I disorder and cigarette smoking, alcoholic beverages, obesity, diabetes, hypertension, lipid profile parameters, hyperhomocysteinemia, hypofolatemia, hypovitamin B12 and, hyperuricemia.

Parameters	Patients (n = 130)	Controls (n = 175)	OR	IC 95%	p	OR*	p*
Cigarette smoking	52.3%	39.4%	1.68	1.06-2.66	**0.025**	-	-
Alcoholic beverages	13.1%	6.9%	2.04	0.94-4.44	0.067	-	-
Obesity (BMI ≥ 30 kg/m²)	33.1%	8%	5.68	2.94-10.96	**< 0.001**	8.69	**< 0.001**
Diabetes ≥ *6.1 mmol/L*	16.1%	9.7%	1.79	0.90-3.55	0.092	1.60	0.325
Hypertension (≥ 130/85 mm Hg)	5.4%	16%	0.34	0.15-0.78	0.008	0.43	0.136
Hypercholesterolemia (≥ 5.17 mmol/L*)*	26.2%	26.9%	0.96	0.57-1.61	0.891	0.99	0.987
Hypertriglyceridemia (≥ 1.7 mmol/L)	53.1%	17.7%	4.10	2.44-6.90	**< 0.001**	3.71	**< 0.001**
HyperLDL (≥ 3.4 mmol/L)	13.1%	26.9%	0.39	0.22-0.73	0.002	0.48	< 0.001
¥*HypoHDL*	59.2%	58.3%	1.00	0.63-1.59	0.975	0.78	0.359
HyperLp(a) (≥ 200 mg/L)	47.7%	14.8%	5.25	3.04-9.07	**< 0.001**	4.48	**< 0.001**
Hyperhomocysteinemia (≥15 µmol/L)	39.2%	18%	2.80	1.66-4.72	**< 0.001**	1.95	**0.038**
Hypovitamin B12 (< 187 ng/L)	21.2%	14.9%	0.69	0.34-1.38	0.296	0.62	0.215
Hypofolatemia (< 3.7 µg/L)	66.2%	36.2%	3.44	2.13-5.54	**< 0.001**	3.69	**< 0.001**
£*Hyperuricemia*	10.8%	4.4%	2.05	0.71-5.91	0.176	1.58	0.439

* Lipid profile parameters, folatemia, vitamin B12 and uric acid were adjusted for gender, BMI, cigarette cigarette smoking, alcoholic beverages, diabetes and hypertension; * Hcys was adjusted for gender, BMI, cigarette smoking, alcoholic beverages, diabetes, hypertension, folatemia and vitamin B12; *Diabetes was adjusted for gender, BMI, cigarette smoking, alcoholic beverages, hypertension and dyslipidemia; *Obesity was adjusted for gender, cigarette smoking, alcoholic beverages, hypertension, diabetes and dyslipidemia; *Hypertension was adjusted for gender, cigarette smoking, alcoholic beverages, diabetes and dyslipidemia; \ c-HDL <1.1 mmol/L (in men) and < 0 .9 (in women); £ uric acid: 210-420 µmol/L (in men) and 150-360 µmol/L (in women)

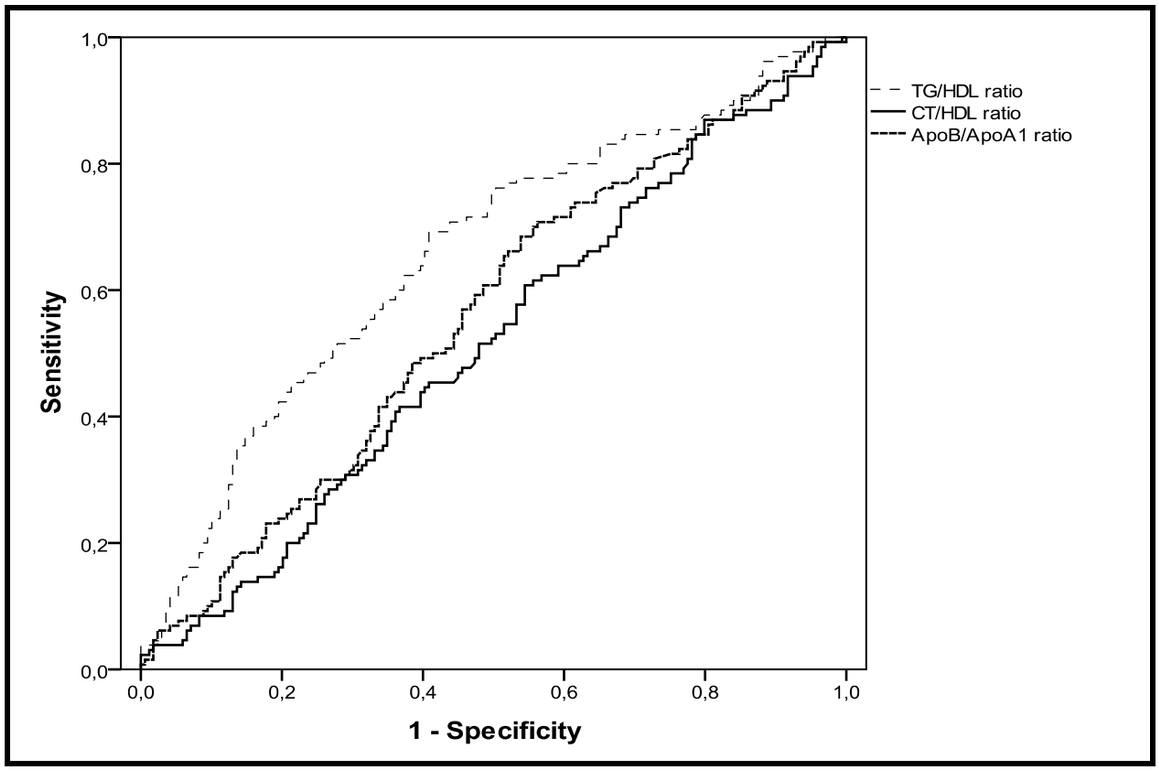
Table 4. Association between bipolar I disorder and cigarette smoking, alcoholic beverages, obesity, diabetes, hypertension, lipid profile parameters, hyperhomocysteinemia, hypofolatemia, hypovitamin B12, and hyperuricemia.

We showed significant association between bipolar I disorder and some cardiovascular risk factors: obesity (33.1% *Vs* 8%, OR = 5.68, IC 95% = 2.94-10.96; p < 0.001), hyperLp(a) (47.7% *Vs* 14.8%, OR = 5.25, IC 95% = 3.04-9.07; p < 0.001), hypertriglyceridemia (53.1% *Vs* 17.7%, OR = 4.10, IC 95% = 2.44-6.90; p < 0.001), hypofolatemia (66.2% *Vs* 36.2%, OR = 3.44, IC 95% = 2.13-5.54; p < 0.001), hyperhomocysteinemia (39.2% *Vs* 18%, OR = 2.80, IC 95% = 1.66-4.72; p < 0.001) and cigarette smoking (52.3% *Vs* 39.4%, OR = 1.68, IC 95% = 1.06-2.66; p = 0,025). After adjustment for potential confounder factors, these associations remained significant (table 4).

Alcoholic beverage, diabetes and hyperuricemia were not significantly associated with this illness but we showed that they were more frequents in patients than controls (13.1% *Vs* 6.9%, p = 0.067; 16.1% *Vs* 9.7%, p = 0.325; 10.8% *Vs* 4.4%, p = 0.439; respectively). Additionally, the risk of diabetes and hyperuricemia were respectively multiplied by 1.5 in patients (16.1% *Vs* 9.7%, OR = 1.60, IC 95% = 0.62-4.12; p = 0.325; 10.8% *Vs* 4.4%, OR = 1.58, IC 95% = 0.49-5.08; p = 0.439) and the risk of alcoholic beverage by two (13.1% *Vs* 6.9%, OR = 2.04, IC 95% = 0.94-4.44; p = 0.067) (table 4).

On the contrary, this disease was not associated with hypertension (5.4% *Vs* 16%, OR = 0.43, IC 95% = 0.14-1.29; p = 0.136) nor with hyperLDL (13.1% *Vs* 26.9%, OR = 0.48, IC 95% = 2.53-7.95; p < 0.001) (table 4).

Fig.1. illustrates the receiver Operating Characteristic (ROC) of three index of atherogenicity as predictive factors of cardiovascular risk.



TG: triglycerides; CT: cholesterol

Fig. 1. Receiver Operating Characteristic (ROC) of three index of atherogenicity as predictive factors of cardiovascular risk.

The specificity and sensibility of three index of atherogenicity as predictive factors of cardiovascular risk are shown in table 5.

Parameters	AUC (95% CI)	Cut off	Specificity	Sensibility	p
TG/HDL	0.65 [0.59-0.71]	1.12	0.63	0.62	**< 10^{-3}**
CT/HDL	0.52 [0.44-0.57]	3.93	0.53	0.57	0.661
ApoB/ApoA1	0.56 [0.49-0.62]	0.66	0.54	0.55	0.070

TG: triglycerides; CT: cholesterol; AUC; Area under the curve

Table 5. Specificity and sensibility of three index of atherogenicity as predictive factors of cardiovascular risk

Fig. 2. Illustrates the Receiver Operating Characteristic (ROC) of Lp(a) and homocysteine as predictive factors of cardiovascular risk.

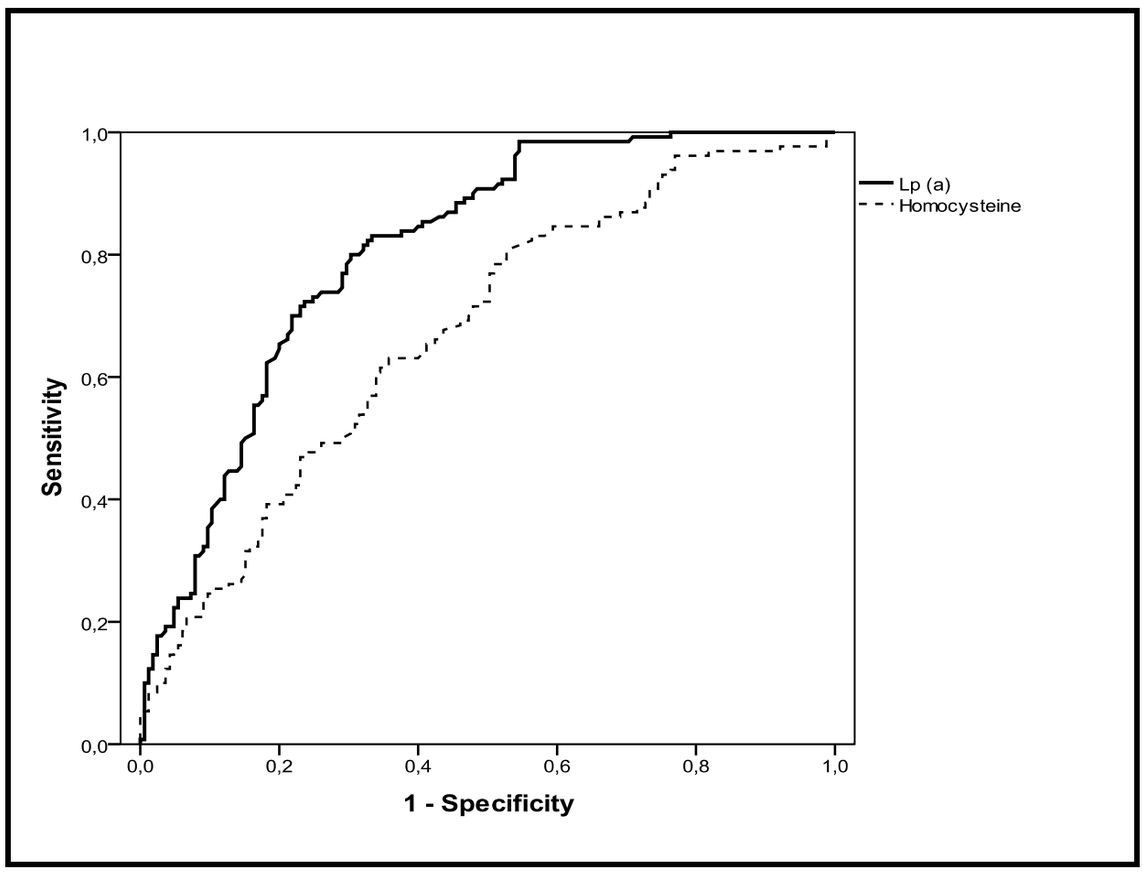


Fig. 2. Receiver Operating Characteristic (ROC) of Lp(a) and homocysteine as predictive factors of cardiovascular risk.

Table 6 reports the specificity and sensibility of Lp(a) and homocysteine as predictive factors of cardiovascular risk.

Parameters	AUC (95% CI)	Cut off	Specificity	Sensibility	p
Lp(a) (mg/L)	0.80 [0.75-0.85]	168	0.75	0.74	**$< 10^{-3}$**
Homocysteine (µmol/L)	0.52 [0.44-0.57]	13.4	0.60	0.62	**$< 10^{-3}$**

AUC; Area under the curve

Table 6. Specificity and sensibility of Lp(a) and homocysteine as predictive factors of cardiovascular risk.

TG/HDL ratio and Lp(a) were found as the best predictive factors of cardiovascular risk in terms of sensibility (0.62, 0.74; respectively) and specificity (0.63, 0.75; respectively) at threshold of 1.12 and 168 mg/L, respectively (tables 5, 6; fig 1, 2).
The prevalence of metabolic syndrome (modified NCEP-ATP III) and its profile in bipolar I patients are shown in table 7.

	N	%
Total of the association of 5 criteria	**2**	**5.9**
Diabetes, Obesity, Hypertriglyceridemia, Low c-HDL	1	
Diabetes, Obesity, Low c-HDL, High blood pressure	1	
Diabetes, Hypertriglyceridemia, Low c-HDL, High blood pressure	1	
Total of the association of 4 criteria	**3**	**8.8**
Obesity, Hypertriglyceridemia, Low c-HDL	15	
Diabetes, Low c-HDL, Hypertriglyceridemia	6	
Obesity, Hypertriglyceridemia, Diabetes	4	
Obesity, Hypertriglyceridemia, High blood pressure	2	
Diabetes , High blood pressure, Obesity	1	
Hypertriglyceridemia, Low c-HDL, High blood pressure	1	
Total of the association of 3 criteria	**29**	**85.3**
At least three or more criteria	**34**	**100**

Table 7. Prevalence of metabolic syndrome (modified NCEP-ATP III) and its profile in bipolar I patients.

The prevalence of metabolic syndrome in bipolar I patients was 26.1% (N = 34). The highest prevalence of this syndrome was obtained by the association between obesity, low c-HDL and hypertrilyceridemia (44.1 %) (Table 7).
Table 8 reports the Prevalence of the components of metabolic syndrome in the total sample of bipolar I patients.

Criteria	N (%)
c-HDL < 1.1 mmol/L (men) and < 0 .9 (women)	**77(59.2)**
TG ≥ 1.7 mmol/L	**69(53.1)**
BMI ≥ 28.5 kg/m²	**44 (33.8)**
Fasting blood glucose ≥ 6.1 mmol/L	**21 (16.1)**
Blood pressure ≥ 130/85 mm Hg	**7(5.4)**

Table 8. Prevalence of the components of metabolic syndrome in the total sample (N=130).

The prevalence of individual diagnostic components, in the total sample, was as follows: 59.2% for low c-HDL, 53.1% for hypertriglyceridemia, 33.8% for obesity (BMI ≥ 28.5 kg/m²), 16.1% for high fasting glucose and 5.4% for hypertension (Table 8).
Table 9 reports the characteristics of patients with or without metabolic syndrome.

	With MS [N= 34 (26.1%)]	**Without MS [N= 96 (73.9%)]**	**p values**
Variables	**N (%)**	**N (%)**	
Gender			
Men	21 (24.7)	64 (75.3)	0.60
Women	13 (28.9)	32 (71.1)	
Illness episode			
Depressive	4 (19)	17 (81)	0.651[a]
Euthymic	19 (26)	54 (74)	
Manic	11 (30.5)	25 (69.5)	
Treatment			
Antipsychotics	10 (26.3)	28 (73.7)	0.9574[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 and 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 detected using Fisher's exact test

Table 9. Characteristics of patients with or without metabolic syndrome.

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 *V*s 37.0 ± 12.7 years), but this difference was not significant (table 9).
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 (table 9).
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%) (table 9).
Patients with metabolic syndrome had significantly higher levels of uric acid ($p < 0.001$) than metabolic syndrome free patients (table 9).
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 (table 9).

The variations of lipid profile parameters according to the illness episode and therapeutic characteristics of bipolar I patients are shown in table 10.

	Triglycerides (mmol/L)	**Cholesterol (mmol/L)**	**c-HDL (mmol/L)**		**c-LDL (mmol/L)**	**Lp (a) (mg/L)**	**ApoB/Apo A1**
			Men	**Women**			
Patients (n = 130)	1.95 ± 1.55	4.42 ± 0.99	1.04 ± 0.37	1.17 ± 0.36	2.14 ± 1.10	243 ± 223	0.71 ± 0.23
Illness episode							
Depressive (n = 21)	1.95 ± 1.32	4.49 ± 0.96	1.12 ± 0.28	0.99 ± 0.36	2.14 ± 1.09	158 ± 91	0.82 ± 0.41
Euthymic (n = 73)	1.94 ± 1,80	4.53± 0.96	1.05 ± 0.41	1.26 ± 0.33	2.18 ± 1.04	268 ± 242	0.68 ± 0.19
Manic (n = 36)	1.97 ± 1.25	4.14 ± 1.0	0.98 ± 0.32	1.10 ± 0.11	2.08 ± 1.25	240 ± 228	0.70 ± 0.26
Treatment							
Valproic acid (n = 64)	1.78 ± 1.20	4.25 ±1.00	1.05 ± 0.40	1.13 ± 0.24	2.11 ± 1.12	240 ± 232	0.70 ± 0.24
Lithium (n = 12)	1.43 ± 0.95	4.40 ± 0.85	1.10 ± 0.36	0.86 ± 0.49	2.17 ± 0.82	170 ± 93	0.78 ± 0.29
Carbamaze pine (n = 10)	2.24 ± 3.25	4.60 ± 1.10	0.97 ± 0.33	1.44 ± 0.40	1.75 ± 0.74	293 ± 221	0.66 ± 0.22
AVP and Li (n =6)	2.33 ± 1.07	3.93 ± 0.40	1.10 ± 0.28	0.79	2.10 ± 1.22	153 ± 69	0.76 ± 0.23
Anti-psychotics (n = 38)	2.26 ± 1.64	4.74 ± 1.00	1.03 ± 0.36	1.26 ± 0.40	2.30 ± 1.23	271 ± 248	0.71 ± 0.30

AVP: valproic acid; Li: lithium

Table 10. Variations of lipid profile parameters according to the illness episode and therapeutic characteristics of bipolar I patients.

Our study failed to show any significant association between lipid profile parameters, illness episode and treatment, while euthymic patients were found to have the highest levels of Lp(a) and depressive patients had the highest levels of ApoB/ApoA1 ratio (table 10). Additionally, we showed that women taking lithium had the lowest c-HDL values and patients taking carbamazepine had the highest values of Lp(a) (table 10).

Table 11 reports the variations of uric acid, homocysteine, folate and vitamin B12 concentrations according to the illness episode and therapeutic characteristics of bipolar I patients.

	Uric acid (µmol/L)		**Homocysteine (µmol/L)**	**Folate (µg/L)**	**Vitamin B12 (ng/L)**
	Men (n = 85)	**Women (n = 45)**			
Patients (n = 130)	311 ± 99	246 ± 97	15.8 ± 8.9	3.3 ± 0.9	356 ± 198
Illness episode					
Depressive (n = 21)	228 ± 79	205 ± 128	15.2 ± 6.7	3.4 ± 1.3	481 ± 299[a]
Euthymic (n = 73)	309 ± 110	271 ± 95	16.1 ± 10.1	3.4 ± 0.7	322 ± 165
Manic (n = 36)	327 ± 87	217 ± 57	15.5 ± 7.7	3.3 ± 1.2	352 ± 158
Treatment					
V*alproic acid* (n = 64)	328 ± 91	279 ± 109	16.3 ± 10.0	3.5 ± 0.9	361 ± 91
Lithium (n = 12)	331 ± 79	219 ± 88	17.1 ± 12.7	2.8 ± 0.6	399 ± 79
Carbamazepine (n = 10)	278 ± 160	207± 61	16.9 ± 9.4	3.2 ± 0.8	240 ± 160*
AVP and Li (n = 6)	343 ± 76	288	15.5 ± 2.9	3.0 ± 0.8	518 ± 236*
A*ntipsychotics* (n = 38)	269 ± 96	218 ± 83	14.2 ± 5.9	3.4 ± 1.5	338 ± 233

AVP: valproic acid; Li: lithium; *Carb Vs AVP/Li, p = 0.04; [a]$F_{2\text{-}130}$ = 5.688, p = 0.004

Table 11. Variations of uric acid, homocysteine, folate and vitamin B12 concentrations according to the illness episode and therapeutic characteristics of bipolar I patients.

We found a significant association between vitamin B12 values and illness episode ($F_{2\text{-}130}$ = 5.688, p = 0.004). Manic patients had lower values of this parameter than depressive patients. Moreover, we showed that vitamin B12 was significantly associated with the therapeutic characteristics. Indeed, patients taking carbamazepine had significantly lower values of this parameter than those taking valproic acid and lithium (p = 0.04) (table 11).
In patients, there was no significant change in homocysteine, folate and uric acid values in relation to illness episodes and the treatment, whereas the lowest values of uric acid were seen in depressive patients (both in men and women) compared to manic patients and in men taking antipsychotics and women taking carbamazepine compared to the other groups (table 11).
The distribution of BMI according to the illness episode and therapeutic characteristics is shown in table 12.

Our study failed to show any significant association between the BMI and to the illness episode and, therapeutic characteristics. However, we found that obesity was more frequent in depressive patients than in those with manic episode (38.1% *Vs* 27.8%). In addition, obesity and overweight were more frequent (72% and 52%; respectively) in patients taking valproic acid or lithium (table 12).

BMI (kg/m²) **Characteristics**	**BMI ≥ 30** **n = 43 (%)**	**25 ≤ BMI < 30** **n = 40 (%)**	**BMI** **< 25** **n = 47 (%)**
Illness episode			
Depressive (n = 21)	8 (38.1)	4 (19.1)	9 (42.8)
Euthymic (n = 73)	25 (34.2)	23 (31.5)	25 (34.3)
Manic (n = 36)	10 (27.8)	13 (36.1)	13 (36.1)
Treatment			
Valproic acid (n = 64)	25 (39.1)	17 (26.6)	22 (34.3)
Lithium (n = 12)	6 (50)	4 (33.3)	2 (16.7)
Carbamazepine (n = 10)	2 (20)	5 (50)	3 (30)
AVP and Li (n = 6)	2 (33.3)	3 (50)	1 (16.7)
Antipsychotics (n = 38)	8 (21.1)	11 (28.9)	19 (50)

AVP: valproic acid; Li: lithium

Table 12. Distribution of BMI according to the illness episode and therapeutic characteristics.

4. Discussion

Our study showed that patients had significantly higher levels of triglycerides and Lp(a), and significantly lower levels of ApoA1 than control subjects. Furthermore, bipolar I disorder was showed to have significant association with hyperLp(a) (47.7% *Vs* 14.8%, OR = 4.48, IC 95% = 2.53-7.95; $p < 0.001$) and hypertriglyceridemia (53.1% Vs 17.7%, OR = 3.71, IC 95% = 2.13-6.46; $p < 0.001$).

In patients, the TG/HDL ratio and Lp(a) were found as the best predictive factors of cardiovascular risk in terms of sensibility (0.62, 0.74; respectively) and specificity (0.63, 0.74; respectively) at threshold of 1.12 and 168 mg/L, respectively. These results reflect a high risk of cardiovascular disease and may explain the high rates of morbidity and mortality in this population. Several studies have found mortality rates between 1.5 and 2.5 times higher in bipolar patients than the general population. After suicide and accidents, cardiovascular and all vascular diseases are the leading causes of death in these patients, with standardized mortality ratios ranging from 1.47 to 2.6. (Garcia-Portilla et al., 2009; Sicras et al., 2008).

The exact mechanisms increasing the incidence of cardiovascular risk in bipolar patients remain to be clarified, but they possibly include industrialisation, stress, lack of exercise, dietary lipids (that is, omega-3 fatty acid deficiency), increasing incidence of smoking and alcohol consumption and other factors (Ezzaher et al., 2010). These hypotheses will be, in part, justified later in this study.

Several investigators have been hypothesized that abnormalities in fatty acid composition may play a role in psychiatric disorders (Horrobin & Bennett, 1999). Maes et al. (1996, 1999) reported that patients with major depression had a significantly elevated ratio of ecosapentaenoic acid (EPA; 20: 5n-3)/docosahexaenoic acid (DHA; 22: 6n-3), lower level of EPA and total n-3 Omega-3 polyunsaturated fatty acids, in both serum cholesteryl esters and phospholipids when compared to patients with minor depression and normal controls. Similar findings were revealed in terms of fatty acid compositions of the erythrocyte membrane (Adams et al., 1996; Edwards et al., 1998; Peet et al., 1998; Chiu et al., 2003).

Moreover, many prospective and case-control studies have shown a positive association between serum triglycerides and coronary artery disease risk and demonstrated the importance of fasting triglycerides level as an independent risk factor. A number of clinical trials including the Framingham Heart Study have concluded that a low HDL cholesterol level predicts the risk for coronary artery disease independently of other risk factors. Each 1 mg/dL decrease in HDL cholesterol has been shown to increase risk for coronary artery disease by 2% in men and 3% in women. The Veterans Affairs High-Density Lipoprotein Cholesterol Interventional Trial, investigating the impact of fibrate therapy on cardiovascular risk, demonstrated that 6% increase in HDL cholesterol was associated with a 22% decrease in coronary events (Kabakci et al., 2008). In addition, Lp(a) has been shown to be an independent risk factor for atherosclerosis (Hakim et al., 2008) and has been found to exert a broad variety of pro-atherogenic and pro-thrombotic properties (von Eckardstein et al., 2001). Elevated plasma Lp(a) has been shown also to be associated with premature cardiovascular disease, premature cerebrovascular disease and premature peripheral vascular disease (Valentine et al., 1996).

The underlying mechanism for the altered lipid status in bipolar patients is unclear. A possible explanation might be found in the patient's nutritional status, the decrease in physical activity and the medications used (Ezzaher et al., 2010). Additionally, Chung et al. (2007) reported that bipolar disorder is associated with perturbations in lipid profile which play an important role in the pathophysiology of mood disorders, particularly in bipolar disorders. Indeed, cholesterol is one component of circulating lipoprotein particles that, besides handling cholesterol, carries micronutrients such as vitamins A and E as well as triglycerides and phospholipids. The latter compounds give rise to substrates such as fatty acids and choline, which are used in both the structural lipids of neuronal membranes and intercellular communication. Therefore, higher levels of one or more compounds of lipoprotein particles circulating in the bloodstream may produce subtle but measurable enhancements of mental processes by influencing the supply of fat-soluble micronutrients, specific fatty acids, or structural lipids (Ezzaher et al., 2010).

Our study failed to found any significant association between lipid profile parameters and illness episode, while euthymic patients were found to have the highest levels of Lp(a). Additionally, depressive patients had the highest levels of ApoB/Apo A1 ratio. However, some authors (Sagud et al., 2009) showed that serum cholesterol and LDL values were significantly lower in manic patients and others (Chung et al., 2007) showed that there was no difference in mean serum level of cholesterol or triglycerides among patients with

manic, mixed, or depressive episode. These differences could be due to ethnicity and eating habits.

About therapeutic characteristics, any significant association was shown between lipid profile parameters and treatment, while, women taking lithium had the lowest c-HDL values and patients taking carbamazepine had the highest values of Lp(a). The mechanism(s) by which these drugs exert weight gain are not well known, but are presumed to involve increased energy intake (e.g., overeating), decreased energy expenditure (e.g., reduced resting metabolic rate, reduced physical activity, or reduced diet-induced thermogenesis), or a combination of the two (Malhotra & McElroy, 2002).

Additionally, we found that the prevalence of metabolic syndrome was 26.1% among patients, 24.7% in men and 28.8% 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 criteria (Bouguerra et al., 2006).

Compared with other studies, the prevalence of metabolic syndrome in our patients is included between those in Spanish patients (22.4%), Italian patients (25.3%) and US patients (30%) (Garcia-Portilla et al., 2008; Salvi et al., 2008; Fagiolini et al., 2005). The increasing prevalence of metabolic syndrome is important because it confers greater cardiovascular morbidity and mortality. Prospective observational studies have demonstrated an association between metabolic syndrome and development of type II diabetes (Hanson et al., 2002; Resnick et al., 2003; Klein et al., 2002; Sattar et al., 2003), cardiovascular disease (Lakka et al., 2002; Kip et al., 2004), and stroke (Kurl et al.,2006).

Our study showed that the highest prevalence of metabolic syndrome was obtained by the association between obesity, low c-HDL and hypertriglyceridemia. Moreover, the most individual components of this syndrome, in the total sample of patients, was low c-HDL (59.2%), hypertriglyceridemia (53.1%) and obesity (BMI ≥ 28.5 kg/m²) (33.8%), confirming in part the higher risk of dyslipidemia and obesity in bipolar I patients and in other hand the higher risk of cardiovascular disease in this population.

We found no significant difference in the prevalence of metabolic syndrome among gender and age. This is in line with results reported by Yumru et al., (2007).

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 one (Murray et al., 2009). Additionally, Angst et al. (2002) 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 Casey, lithium has been shown to stimulate appetite and increase calorie intake through different mechanisms.

HOMA-IR is significantly higher 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 factors (Toalson et al., 2004). In addition, uric acid levels were significantly higher in patients with metabolic syndrome. According to Vuorinen-Markkola et al. (1994), hyperuricemia forms another consistent feature of the metabolic syndrome what led to the suggestion of uric acid being a new component of the syndrome.

In addition, Chien et al., (2008) 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 oxid production, and consequently, makes peripheral tissue resistant to insulin effects and results in endothelial dysfunction (Chien et al., 2008). High levels of uric acid are associated with increased renal glomerular pressure and sodium reabsorption, enhanced by high insulin concentrations (Alkerwi et al., 2009). In addition, hyperuricemia was associated with insulin resistance markers, including triglycerides, microalbuminuria and impaired glucose tolerance. These disturbances contribute to increase cardiovascular risk (Chien et al., 2008). This insulin- resistance causes steatosis, which is associated with hyper secretion of hepatic enzymes (Fromenty et al., 2004).

In men, uric acid was significantly higher in patients than controls. Additionally, the risk of hyperuricemia in bipolar I patients was approximately multiplied by 1.5 (10.8% *Vs* 4.4%, OR = 1.58, IC 95% = 0.49-5.08; p = 0.439). Many, but not all, epidemiological studies have suggested that high plasma uric acid is a risk factor for cardiovascular diseases. This raised level of plasma uric acid, parallel to an increased risk of cardiovascular diseases, could be either primary or secondary to the underlying causes of the cardiovascular diseases. However, the specific role of plasma uric acid in this constellation remains uncertain, although it may be involved in the platelet adhesiveness, aggregation, or inflammation and it may be implicated in the genesis of hypertension. In contrast, there is some evidence that the increase of plasma uric acid is protective against the cardiovascular diseases, since uric acid acts as an endogenous antioxidant, and the higher plasma uric acid levels found in cardiovascular diseases patients suggest that any protective antioxidant effect of uric acid is hidden by other negative effects in these pathogeneses (Haj mouhamed et al., 2010).

Additionally, Torres et al. (2007), reported that hyperuricemia which implicated in the oxidative stress plays an important role in the pathophysiology of bipolar disorders. The idea that the purinergic system might be involved in bipolar disorder dates back to Kraepelin, who was the first to describe an association between manic symptoms, uric acid excretion, hyperuricemia, and gout. In fact, the purinergic system modulates sleep, motor activity, cognition, attention, behavior, and mood. Even in the absence of a psychiatric diagnosis, individuals with higher uric acid levels are more likely to show higher drive, disinhibition, hyperthymia, or irritable temperament (Lorenzi et al., 2010). Similarly, diseases characterized by purinergic turnover dysfunction and uric acid overproduction (e.g., Lesch–Nyhan syndrome) are associated with impulsive/aggressive behavior, disinhibition, and increased sexual drive (Salvadore et al., 2010).

Among clinical and therapeutic characteristics, we found that there was no significant change in uric acid values in relation to illness episodes and the treatment. This finding is not in agreement with the previous studies that reported that plasma uric acid levels were

higher only during the manic phase of bipolar disorder but not during the depressive or euthymic phases (De Berardis et al., 2008). Additionally, lithium was found to low uric acid plasma levels and to have uricosuric effects in mania. Carbamazepine and phenytoin similarly decreased uric acid levels; in contrast, valproate appeared to have the opposite effect. However, it is important to note that the effect of these drugs on uric acid levels in relationship to clinical improvement in patients with bipolar disorder has not been systematically evaluated (Salvadore et al., 2010).

Compared with controls, patients had significantly higher levels of homocysteine and significantly lower levels of folatemia. Additionally, significant associations were showed between bipolar I disorder and hyperhomocysteinemia (39.2% *Vs* 18%, OR = 1.95, IC 95% = 1.04-3.69; p = 0.038) and hypofolatemia (66.2% *Vs* 36.2%, OR = 3.69, IC 95% = 2.20-6.19; p < 0.001). Homocysteine is an intermediary metabolite of the essential amino acid methionine. Folate and vitamin B12 are required for remethylation of homocysteine to methionine (Hankey & Eikelboom, 1999).

According to Reynolds (2006), hyperhomocysteinaemia has long been identified as a risk factor for vascular disease and the lowering of homocysteine concentrations by the treatment with folic acid, or possibly vitamin B12 and vitamin B6 which might reduce the risk of both cardiovascular and cerebrovascular diseases. Moreover, the association between increased circulating homocysteine concentrations and premature vascular thrombotic events in individuals with hereditary homocystinuria is well established. This process may include platelet activation, smooth muscle cell proliferation, and enhanced leukocyte binding to the endothelium. In recent years, a relationship between milder degrees of hyperhomocysteinaemia and vascular disease has emerged, and this has been the subject of intense research. Hyperhomocysteinemia can be caused by a wide range of disorders, the most important of which are genetic defects of the enzymes involved in homocysteine metabolism and/or deficiencies of their co-factors: folate (former vitamin B9), vitamin B12 and vitamin B6 (Haj mouhamed et al., 2011).

Our study showed a significant association between bipolar I disorder and hyperhomocysteinemia. The exact mechanisms underlying the hyperhomocysteinemia in this disease are not completely understood and controversed among studies. Several hypotheses have been postulated including nutritional folate and vitamin B deficiency, and/or reduced glomerular filtration rate in bipolar patients (Vuksan-Ćusa et al., 2011). En effect, we found a significant association between this disease and hypofolatemia. Furthermore, some authors (Atmaca et al., 2005) showed that at a high concentration, homocysteine is considered to be a neurotoxic substance, causing activation of NMDA (N-methyl D-aspartate) receptors and leading to excitotoxicity. By impairing the neural plasticity and promoting neuronal degeneration, homocysteine could contribute to the pathogenesis of neurodegenerative and psychiatric disorders (Ipcioglu et al., 2008). Additionally, homocysteine is a methyl donor when activated to S-adenosylmethionine. So aberrant DNA methylation due to hyperhomocysteinemia also may be involved in the pathogenesis of bipolar disorder as well as schizophrenia (Mill et al., 2008).

In the other hand, folate appears to influence the synthesis rate of tetrahydrobiopterin, a cofactor in the hydroxylation of phenylalanine and tryptophan, rate-limiting steps in the biosynthesis of dopamine, norepinephrine, and serotonin, neurotransmitters postulated to play a role in the monoamine hypothesis of affective disorders. In addition, methyl tetrahydrofolate has been shown to bind to presynaptic glutamate receptors, where it may

potentially modulate the release of other neurotransmitters, including the monoamines (Atmaca et al., 2005).

Moreover, some studies showed that lower folatemia in patients with psychiatric disorders can be due to their nutritional status (Reif et al., 2005). Indeed, poor appetite as a symptom of bipolar disorder could lead to decreased intake of B vitamins which could then lead to elevated homocysteine concentrations (Tolmunen et al., 2004).

We found a significant association between vitamin B12 values and illness episode. Manic patients had lower values of this parameter than depressive patients. This can be explained by the eating habits of bipolar patients. Indeed, Parikh et al. (2000) found that manic episode is often associated with weight loss.

About therapeutic characteristics, we showed that only vitamin B12 was significantly associated with the medication use. Indeed, patients taking carbamazepine had significantly lower values of this parameter than those taking valproic acid and lithium. These findings are not in agreement with others studies. In fact, Derkes and Westphal (2005) showed that carbamazepine can cause elevated homocysteine concentrations. Although, according to Ozbek et al (2008), homocysteine, folate and vitamin B12 were not related to drug usage. Additionally, Osher et al (2008) reported that there were no significant differences in homocysteine levels between patients receiving versus not receiving lithium, neuroleptic or valproate. However, Sener et al. (2006) suggested that carbamazepine, as enzyme inducer, can directly modulate the activity of different liver enzymes. Liver enzyme induction may cause depletion of the cofactor involved, folic acid, pyridoxal 5'-phosphate and vitamin B12, leading to the alterations in homocysteine status.

Our study showed that bipolar I patients are so much more likely to be smokers than controls (52.3% *Vs* 39.4%, OR = 1.68, IC 95% = 1.06-2.66; p = 0.025). An association between smoking and bipolar I disorder has been established and prevalence rates for lifetime and current smoking have been shown to be as high as 82.5% and 68.8% respectively (Lasser et al., 2000). The possible explanations for the high rates of smoking include an increased genetic vulnerability, a greater susceptibility to addiction because of a greater subjective experience of reward or pleasure, or that tobacco helps relieve some of the symptoms related to a behavioural disorder. For example, cigarette smoking may be an attempt to self-medicate symptoms of depression, anxiety, boredom or loneliness. Other possible explanations for continuing to smoke include increased withdrawal symptoms and reduced side effects from psychiatric medication (Williams & Ziedonis, 2004). Additionally, it has been reported that nicotine stimulates the brain to release dopamine, which is associated with pleasurable feelings, and smokers quickly develop regular smoking patterns. Eventually, smokers need increasing levels of nicotine to feel 'normal'. In the other hand, cigarette smoking is known to contribute to many diseases, including cancer, chronic obstructive pulmonary disease, stroke, cardiovascular diseases, and peptic ulcers. Investigators have attempted to elucidate the mechanisms of the pathogenesis associated with cigarette smoking, but the conclusions were not consistent. A basic hypothesis is that free radicals cause oxidative damage to macromolecules such as lipids, proteins, and DNA. Therefore, these radicals play an important role in the pathogenesis of these diseases (Haj mouhamed et al., 2010).

In this study, the prevalence of obesity is higher in patients with bipolar I disorder than in controls. Moreover, the risk of obesity in these patients is approximately multiplied by nine (33.1% *Vs* 8%, OR = 8.69, IC 95% = 3.61-20.87; p < 0.001).

In bipolar I patients, the prevalences of obesity and overweight were respectively 33.1 % and 30.7 %. These findings were similar to those reported by Elmslie et al (2000) and Fagiolini et al (2002) (36 % and 32 %). However, higher values were reported by McElroy et al (2004) (44 % and 20 %).

For this population, we found that the prevalence of obesity greatly exceeded that found in controls (12.3%) and in the general population (20%) (Haddad et al., 2006). Obesity in patients with bipolar I disorder thus constitutes a major public health problem and suggests that the development and testing of specific interventions that target the obesity epidemic in this particular population are urgently needed. Bipolar disorder and obesity both have tremendous impact on the physical and mental well-being of affected individuals. Therefore, both illnesses should be treated with a coordinated intensive and multifaceted treatment (Fagiolini et al., 2003).

Moreover, the risk of obesity in these patients is approximately multiplied by nine (33.1% *Vs* 8%, OR = 8.69, IC 95% = 3.61-20.87; $p < 0.001$). This could be one of the missing factors in understanding the relationship between psychiatric disorders and increased cardiovascular risk. In fact, some studies have reported that psychiatric disorders, particularly bipolar disorder, are significantly associated with adverse cardiovascular events and coronary heart disease (Garcia-Portilla et al., 2009). The mechanisms through which obesity leads to coronary heart disease remain hotly debated, but the accumulation, particularly, of visceral fat is widely favoured as the primary mechanism, leading, through the release of fatty acids and other mediators, to insulin resistance, dyslipidaemia, and a pro-inflammatory state. However, obesity in general, and central obesity in particular (ie. excessive visceral intra-abdominal fat) have been under-recognised as risk factors for coronary heart disease in the population, where most attention has been placed on smoking and cholesterol (Pinkney, 2001).

According to Raji et al (2009), the cardiovascular afflictions including obesity, diabetes, hypertension and stroke increase the risk for cognitive decline and dementia, but it is unknown whether these factors, specifically obesity and type 2 diabetes mellitus, are associated with specific patterns of brain atrophy. Obesity and type 2 diabetes mellitus may amplify the risk for dementia by worsening cerebral atrophy even in cognitively intact individuals, raising their vulnerability to future Alzheimer's disease neuropathology.

The same authors, mostly in subjects younger than 65 years, suggest also that increased body tissue fat content (adiposity) is correlated with atrophy in the temporal cortex, frontal lobes, putamen, caudate, precuneus, thalamus, and white matter. It is unknown, but of great interest, whether high tissue fat content, as measured by BMI, is associated with differences in brain structure in cognitively normal elderly (Raji et al., 2009).

Additionally, some studies showed that obesity has psychosocial consequences, including discrimination and stigmatization, which may contribute to the severity of bipolar disorder by negatively impacting patients' general physical health and functioning, quality of life, self-esteem, and psychological well-being. Obese patients have an increased risk of sleep apnea, which causes sleep disruptions and may lead to mood destabilization in patients with bipolar disorder. Obesity may also impact effectiveness of pharmacotherapies by altering the distribution and elimination of medications. Truncal obesity, which is most common, increases the risk of type 2 diabetes mellitus, dyslipidemia, hypertension, stroke, ischemic heart disease, and early death (Cheymol, 2000; Fagiolini et al., 2003; Plante & Winkelman, 2008).

In addition, obesity was more frequent in depressive patients than in those with manic episode (38.1% *Vs* 27.8%). Previous studies reported that patients who had depressive symptomatology were more likely to have excessive caloric and cholesterol intake, to smoke and to be inactive than non-depressed subjects. Another explanation might involve biological mechanisms: it is ascertained that hypothalamic–pituitary- adrenal (HPA) axis dysregulation and high cortisol blood levels lead to increased visceral fat. HPA axis dysregulation has been a common finding in both unipolar and bipolar disorders; recently, some studies reported that increased cortisol blood levels correlated to the amount of intra-abdominal fat in major depression (Maina et al., 2008).

About therapeutic characteristics, we found that obesity and overweight were more frequent (72% and 52%; respectively) in patients taking valproic acid or lithium. These findings are in line with those reported by De Hert et al. (2011). Moreover, Casey et al. (2005) reported that lithium have been shown to stimulate appetite through different mechanisms. The "carbohydrate craving" that is thought to be one of the mechanisms of increased calorie intake in people taking lithium is well known. In addition, it is believed that valproate also stimulates weight gain through a variety of mechanisms, especially the development of insulin resistance and diabetes mellitus type 2. In this line, our study found that this type of diabetes is frequent in patients (16.2%). Additionally, the risk of diabetes is multiplied by 1.5 in patients (16.2% *Vs* 9.7%, OR = 1.60, IC 95% = 0.62-4.12; p = 0.325).

Previous studies suggested that patients with both bipolar disorder and comorbid diabetes have more lifetime psychiatric hospitalizations than patients with bipolar patients without diabetes. The association between these two disorders underscores the importance of screening for diabetes in patients with bipolar illness, particularly because early detection and initiation of treatment to control glycemia may prevent diabetes-related complications. Moreover, other studies have demonstrated cerebrovascular lesions involving small intraparenchymal cerebral vessels and focal infarctions in patients with diabetes. These lesions predominantly occur in areas providing blood supply to the base of the pons, thalamus, and basal ganglia. Diabetes has been implicated as a risk factor for subcortical white-matter lesions observed on magnetic resonance imaging (MRI) scans; similar MRI findings have been noted in patients with bipolar disorder. Cerebral microvascular disease may lead to greater frequency of manic episodes, another reason to minimize diabetes-related complications in patients with comorbid bipolar disorder (Cassidy et al., 1999; Holman et al., 2008).

Alcoholic beverage was not significantly associated with this illness but we showed that it was more frequent in patients than controls (13.1% *Vs* 6.9%, OR = 2.04, IC 95% = 0.94-4.44; p = 0.067). It has been well documented that bipolar disorder and alcoholism commonly co-occur. In fact, the lifetime prevalence of alcohol abuse and drug abuse in people with bipolar disorder are known to be three to nine times more frequent that of the general population (Merikangas et al., 2007; Regier et al., 1990; ten Have et al., 2002).

Additionally, some studies showed that the feelings of depression and anxiety associated with bipolar can be a factor that leads to alcoholism. People with bipolar disorder may use alcohol or other drugs to self medicate these feelings, especially in instances where the person has not been diagnosed. However, alcohol makes the symptoms of bipolar disorder worse. Anyone who shows symptoms of bipolar disorder should seek the advice of medical professionals (Le Strat, 2010).

Some studies have shown that alcohol directly contributes to heart disease and stroke. Heavy drinking raises levels of triglycerides circulating in the bloodstream leading to diabetes and blocked or narrowed arteries that carry blood to the heart. If coronary arteries are clogged with fats, blood cannot flow freely, resulting in heart disease or stroke. Additionally, alcohol directly contributes to heart failure by damaging the heart muscle and arteries. Cardiomyopathy, or an enlargement of the heart muscle, results from long-term alcohol use. An enlarged heart no longer works efficiently and fails to provide enough oxygenated blood to other organs of the body. Furthermore, alcohol is associated with cardiac arrhythmia (irregular heartbeat), sudden cardiac death, stroke and atrial fibrillation (Pearson, 1996).

In our patients, hypertension was not associated with bipolar disorder (5.4% *Vs* 16%, OR = 0.43, IC 95% = 0.14-1.29; p = 0.136). De Heart et al. (2010) explained the decrease of hypertension frequency in individuals with a mental illness by changes in lifestyle of patients such as reducing salt intake.

Several methodological limitations should be considered when interpreting these findings. First, larger sample sizes of groups would be beneficial. Second, our work is a cross-sectional study that does not permit to follow up biological parameters. Third the sample of bipolar patients may not be representative of more heterogeneous populations. Finally, the diagnosis of controls was made by psychiatrists but without formal use of structured instruments to exclude psychiatric disorders in controls.

5. Conclusion

Our results demonstrate that Tunisian bipolar I patients are exposed to higher cardiovascular risk. In fact, they had perturbations in lipid profile: significantly higher values of triglycerides and Lp(a), and significantly lower values of ApoA1, significantly hyperhomocysteinemia and hyperuricemia (in men), significantly hypofolatemia and high prevalence of metabolic syndrome. Obesity, hyperLp(a), hypertriglyceridemia, hypofolatemia, hyperhomocysteinemia and cigarette smoking were the main cardiovascular risk factors associated with bipolar I disorder. Indeed, the risk of obesity was increased approximately for nine once, hyperLp(a), hypertriglyceridemia and hypofolatemia approximately for four once and the other factors approximately for tow once. The TG/HDL ratio and Lp(a) were found as the best predictive factors of cardiovascular risk in terms of sensibility and specificity at threshold of 1.12 and 168 mg/L, respectively.

Our findings noted a significant association between vitamin B12 values and illness episode. Manic patients had lower values of this parameter than depressive patients. Moreover, we showed that vitamin B12 was significantly associated with the therapeutic characteristics. Indeed, patients taking carbamazepine had significantly lower values of this parameter than those taking valproic acid and lithium. Additionally, there was no significant change in homocysteine, folate, uric acid values and metabolic syndrome in relation to illness episode and the treatment, whereas the patients with metabolic syndrome had significant higher levels of HOMA-IR and uric acid than metabolic syndrome free.

Therefore, bipolar I patients require specific care, particularly for lipid profile, vitamin status and weight; the effectiveness of this care will be evaluated during follow-up period Clinicians should track the effects of treatment on physical and the biological parameters, and should facilitate access to appropriate medical care.

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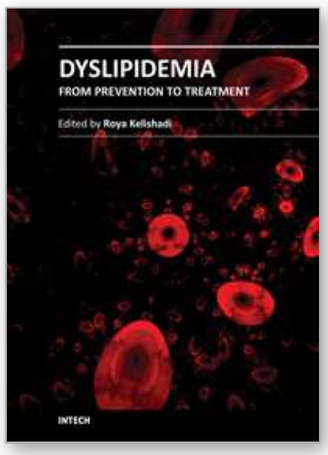

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Dyslipidemia has a complex pathophysiology consisting of various genetic, lifestyle, and environmental factors. It has many adverse health impacts, notably in the development of chronic non-communicable diseases. Significant ethnic differences exist due to the prevalence and types of lipid disorders. While elevated serum total- and LDL-cholesterol are the main concern in Western populations, in other countries hypertriglyceridemia and low HDL-cholesterol are more prevalent. The latter types of lipid disorders are considered as components of the metabolic syndrome. The escalating trend of obesity, as well as changes in lifestyle and environmental factors will make dyslipidemia a global medical and public health threat, not only for adults but for the pediatric age group as well. Several experimental and clinical studies are still being conducted regarding the underlying mechanisms and treatment of dyslipidemia. The current book is providing a general overview of dyslipidemia from diverse aspects of pathophysiology, ethnic differences, prevention, health hazards, and treatment.

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