Does obesity predict bipolarity in major depressive patients?

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ABSTRACT

Background: Differential association of obesity in bipolar and unipolar Major Depressive Episode (MDE) has not been systematically studied. We explore the relationships between obesity and history of manic and hypomanic symptoms in a large national clinical sample of MDE patients.

Method: The sample comprised 571 consecutive patients with a DSM-IV diagnosis of MDE enrolled in a 7 months period. The study involved 30 psychiatric facilities for outpatients, distributed throughout Italy. Diagnosis was formulated by psychiatrists with extensive clinical experience in the diagnosis and treatment of mood disorders. In all patients height (meters) and weight (kilograms) were systematically measured at the moment of the clinical evaluation. The severity of depressive and anxious symptoms was self-evaluated by the means of Zung’s questionnaires for depression and anxiety. For the evaluation of lifetime manic or hypomanic features, Hypomania Check List-32 was also administered.

Results: BMI ≥ 30 was observed in 86 (15.1%) of our MDE patients. The Obese and Non-Obese subgroups did not report differences as regards to age and gender distribution. Obese patients reported a lower number of years of education in comparison with Non-Obese patients. As regards to marital status, Obese patients were more frequently married in comparison with the Non-Obese patients. Obese patients were more frequently belonging to the bipolar group than Non-Obese patients. Obese subjects also reported more frequently than Non-Obese an HCL total score > 14. The effect of educational level, marital status and bipolar-unipolar distinction on the probability of Obese group membership was analyzed by stepwise logistic regression. Bipolar subtype resulted to be the strongest predictor of Obesity.

Limitations: Pharmacological treatments and co-morbidity with other psychiatric disorders are not explored and accounted for in our analyses.

Conclusions: Obesity in our national sample of patients with MDE is associated with bipolar subtype and (hypo)manic symptoms. These findings suggest the possibility that the presence of obesity in patients with MDE might be related to bipolarity. A common impulsive-addictive diathesis is proposed as mediating mechanism. Further longitudinal studies in clinical and non-clinical populations are necessary to better define the burden and the role of the association between obesity and bipolarity.

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1. Introduction

About one third of patients with bipolar disorder (BD) requires more than 10 years from the onset of the first clinical manifestations to the correct diagnosis (Hirschfeld et al., 2003b; Lish et al., 1994; Suppes et al., 2001). The most common incorrect diagnosis is unipolar Major Depressive Disorder (MDD) (Hirschfeld et al., 2003b). According to several epidemiological and clinical studies, almost 40% of BD patients are initially diagnosed with MDD (Ghaemi et al., 1999; 2000) and from 21% to 26% of unipolar depressed patients in primary care settings report some bipolarity aspects after careful screening (Hirschfeld et al., 2005; Manning et al., 1997). These data disclose the age-old diagnostic issue about the implementation of our capacity to immediately give a correct diagnosis. With this purpose during the last decades some clinical features have been identified useful in distinguishing unipolar from bipolar Major Depressive Episode (MDE). Among them earlier age of onset (Lish et al., 1994), positive family history for BD (Bowden, 2005; Hirschfeld et al., 2003a), atypical features (Gold et al., 2002; Perugi et al., 1998), anxiety (Akiskal et al., 2006; Perugi et al., 2003), and substance abuse (Maremmani et al., 2008, 2006) have been observed more commonly in bipolar than unipolar depressive patients.

Obesity is a chronic and relapsing illness which affects from 10% to 35% of the general population (Bray and Bellanger, 2006; Bray and Bellanger, 2006).
Wilborn et al., 2005). In the last decades obesity has become a public health concern due to the increased prevalence rate and the large percentages of morbidity and mortality associated. A relationship between mood disorders and Obesity has been widely demonstrated. Clinical and epidemiologic studies found a positive association between obesity, MDD and BD (Simon et al., 2006), both for men and women, with some gender-mediated differences in psychiatric comorbidity and clinical features. A one-to-one relationship seems to connect affective illnesses and obesity; depressive symptoms, personal and familial history for depressive episodes and high rates of psychological dysfunction are common among treatment-seeking Obese individuals (Johnston, 2004; Heo et al., 2006; Dong et al., 2004) whereas weight gain, overweight and obesity frequently affect the course and the treatment of mood disorders. Fagiolini and colleagues (Fagiolini et al., 2003) observed that obesity is associated with clinical features such as large number of lifetime depressive and manic episodes, severe and difficult-to-treat index affective episode, large amount of affective recurrence, particularly depressive, and short time to relapse. Conversely depression may play an important role in the success of weight loss. Sherwood et al. (2004) found that improvements in binge eating status, mediated by improvement in depression, predicted significantly weight loss in MDD patients.

Interestingly, the risk of depression seems to increase with growing BMI (Onyike et al., 2003). Furthermore, both childhood and adulthood MDD correlate with obesity in adults as in females (Pine et al., 1997, 2001). These results can be explained partly by some clinical overlapping features as overeating, physical inactivity, and high overall carbohydrates intake (Elmslie et al., 2001), partly by comorbid eating disorders as binge-eating disorder (McElroy et al., 2004; Telch and Stice, 1998), and partly by the side-effects of psychotropic medications (Keck and McElroy, 2003). More specifically weight gain, obesity and abdominal obesity are associated with atypical depression (Hasler et al., 2004; Kendler et al., 1996) and BD (Elmslie et al., 2001, 2000) both in males and females and with lifetime hystympanic symptoms in males (Hasler et al., 2004).

To our knowledge the differential prevalence rate in bipolar and unipolar MDE of obesity have not been systematically studied so far. The aim of the present study is to explore the relationships between obesity and history of manic and hystympanic symptoms in a large clinical sample of major depressive patients.

2. Method

COME TO ME is a cross-sectional, multi-center, observational study that enrolled 571 consecutive patients with a diagnosis of Major Depressive Episode, according to DSM-IV, in a 7 months period. The study involved 30 psychiatric facilities for outpatients, distributed throughout Italy; 8 centers are located in north Italy, 9 in central regions, 7 in the south and 6 in the Islands (Sicily and Sardinia). In accordance with the observational nature of the protocol, routine medical procedures were not modified. The Ethics Committee of each center approved the study protocol in compliance with the Italian ministerial bulletin issued on September 2, 2002 regarding observational studies. All patients gave their informed consent concerning handling and use of the data collected during the course of study. The study was sponsored by Boehringher Ingelheim, Italy.

2.1. Study population

Subjects who referred to the selected centers between December 2006 and July 2007 were considered for recruitment in the study. Patients were recruited consecutively according to the following inclusion criteria: (i) men and women aged 18–75 years, (ii) diagnosis of Major Depressive Episode according to DSM-IV (major depressive disorder, recurrent major depression, depressive episode types I and II bipolar disorder, and depression NOS), and (iii) ability to complete the self- and hetero-administered questionnaires. The exclusion criteria were (i) comorbidity with schizophrenia and other psychotic disturbances and (ii) current relevant physical illnesses.

The study included 571 depressed outpatients; 383 subjects (67.1%) were female and, regarding age and 255 subjects (44.7%) were from 18 to 50 years old and 316 (55.3%) over 50. The level of education was higher than 11 years for 246 (43.1%) patients; most of them (n=336, 58.8%) were married.

Diagnostic procedure, clinical evaluation and symptom assessment have been extensively described in the previous reports (Perugi et al., 2011). Diagnosis of MDE (MDD recurrent and single episode, bipolar disorder types I and II, and MDE NOS) was formulated by psychiatrists with extensive clinical experience in the diagnosis and treatment of mood disorders according to DSM-IV criteria. In all patients height (meters) and weight (kilograms) were systematically measured at the moment of the clinical evaluation. The severity of depressive and anxious symptomatology was self-evaluated by the means of Zung’s questionnaires for depression and anxiety (Zung, 1965, 1971). For the evaluation of lifetime manic and hystympanic features, Hypomania Check List-32 (Angst et al., 2005) was also administered.

2.2. Statistics

BMI at the moment of evaluation was calculated. Patients were subdivided into Obese and Non-Obese subgroups on the basis of a ≥ 30 BMI cut off point. Comparisons among the 2 subgroups were conducted by the unpaired Student’s t-test for the dimensional variables and χ² analysis for the categorical ones. The Mann-Whitney u-test and Fisher exact test were utilized when appropriated. We set significance at 0.05 level, two tailed. Effect of the variables resulted significantly different between the two groups in the univariate analyses on probability of Obese group membership was analyzed using multiple stepwise logistic regression, backward procedure. We used the statistical routines of SPSS.

3. Results

Among the 571 valuable patients with MDE, MDD recurrent (n=215, 37.7%) and single episode (n=197, 34.5%) were the most common diagnoses. One hundred and nineteen patients (21.1%) presented Bipolar I or II Depression; moreover, 14 or more hystympanic features, as recorded by means of the HCL-32, were reported by 276 (48.3%) patients. Depression NOS was diagnosed only in 39 (7.0%) patients. The mean severity of depression and anxiety as measured by the means of Zung’s scales was respectively 53.2 (sd=9.3) and 47.2 (sd=10.1).

On the basis of a BMI ≤ 30, 86 (15.1%) were included in the “Obese” and 485 (84.9%) in the “Non-Obese” subgroup. In the Obese subgroup, 24 (27.9%) patients reported a BMI ≥ 35, representing 4.2% of the total sample.

The Obese and Non-Obese subgroups did not report differences as regards to age and gender distribution (Table 1). Obese patients reported a lower number of years of education in comparison with Non-Obese patients (respectively 9.20 ± 4.1 vs. 10.33 ± 4.5, t=-2.30, and p=0.023). Interestingly, the educational level is lowest in the 24 patients with BMI ≥ 35 in comparison with those with BMI between 30 and 35 (n=62) and with Non-Obese subgroup (respectively 7.71 ± 3.3 vs. 9.77 ± 4.3 vs. 10.33 ± 4.5, F=4.31, and p=0.014; the Scheffe F-test: Non-Obese,
BMI30-35 > BMI ≥ 35. As regards to marital status, Obese patients were more frequently married in comparison with the Non-Obese patients (respectively 61, 70.9% vs. 275, 56.7%, \( \chi^2 = 10.38, \text{df} = 2, \text{and } p = 0.009\)).

The two subgroups reported statistically significant differences in demographic distribution according to DSM-IV-TR. Obese patients were more frequently belonging to the bipolar group than Non-Obese subgroup (respectively 61, 70.9% vs. 275, 56.7%, \( \chi^2 = 10.38, \text{df} = 2, \text{and } p = 0.009\)). Interestingly, the rate of bipolarity is greatest patients with BMI ≥ 35 in comparison with those with BMI between 30 and 35 and with Non-Obese subgroup (respectively 10, 41.7% vs. 17, 27.4% vs. 92, 19.0%, \( \chi^2 = 6.84, \text{df} = 2, \text{and } p = 0.009\)).

Obese subjects also reported more frequently than Non-Obese an HCL total score > 14 (respectively 52, 60.5% vs. 224, 46.2%, \( \chi^2 = 5.97, \text{df} = 2, \text{and } p = 0.014\)); the mean number of lifetime (hypo)manic symptoms, measured by HCL-32 total score, was higher in Obese than in Non-Obese patients as well (mean ± sd scores respectively 14.63 ± 8.1 vs. 12.29 ± 8.13, \( \chi^2 = 4.26, \text{and } p < 0.014\)).

Using stepwise logistic regression, we studied the effect of educational level, marital status and bipolar–unipolar distinction, which resulted significantly different between the two groups in the univariate analyses, on the probability of Obese group membership; we excluded HCL-32 because it was largely overlapping with unipolar–bipolar diagnostic classification. Bipolar subtype resulted as the strongest predictor of obesity (OR=2.2, 95% CI=1.30–3.70, and \( p = 0.003\)).

### 4. Discussion

In our national sample of 572 patients, representative of MDE population observed in outpatient psychiatric facilities distributed throughout Italy, obesity is very common, with a prevalence rate of 15.1% in comparison 9.1% observed in Italian general population (ISTAT, 2001). This finding supports the strong association between depression and obesity which is widely reported in the previous studies (Stunkard and Allison, 2003; Faith et al., 2002; Elmslie et al., 2001, 2000, Pine et al., 1997).

In our sample we did not observe a relationship between obesity, age and gender distribution as reported by some authors (Roberts et al., 2003, 2000, 2002; Simon et al., 2006). Obese individuals reported lower educational level when compared with Non-Obese patients; a negative relationship between years of education and severity of obesity was also observed. Patients with BMI > 35 (representing the 4.2% of our sample) reported the lowest number of years of education. This finding is consistent with the studies conducted since 1960s (Pickering et al., 2007; Sobal and Stunkard, 1989). By contrast with majority of the studies (Roberts et al., 2003, 2000, 2002; Simon et al., 2006), we found Obese subjects more frequently married than Non-Obese. Finally we did not find any association with tobacco use.

Interestingly, we observed a strong association between BD and obesity; 31.4% of the Obese subjects were diagnosed as BD in comparison with 19.0% of the Non-Obese. We also found a relationship between severity of the Obesity and rate of bipolarity;
indeed 41.7% of patients with BMI > 35 were diagnosed as BD. The association with history of mania and hypomania is confirmed by the scores of HCL-32 (Angst et al., 2005), 60.5% of the Obese patients reported HCL total score > 14 and the highest mean number of (hypo)manic symptoms was reported by patients with BMI > 35. This finding is consistent with the previous reports (Hasler et al., 2004). In particular, a recent clinical study (Alciati et al., 2007), utilizing HCL-32 in a sample of consecutive Obese patients candidates for bariatric surgery, found a diagnosis of bipolar spectrum in 89% of the sample.

Other research focused on the prevalence of overweight and obesity in bipolar patients, showing comorbidity rates ranging from 20% to 32% (Elmslie et al., 2001, 2000; Fagiolini et al., 2002; McElroy et al., 2002). The majority of patients interviewed assumed many pharmacologic agents associated with weight gain, but no more specific data are available to define how much psychotropic medications are associated with overweight in bipolar patients (Keck and McElroy, 2003).

The specific association between BD and obesity can be partly explained by overlapping symptoms; bipolar depression may include atypical features such as increased appetite, overeating, reduced physical activity and weight gain (Gold et al., 2002; Perugi et al., 1998). Atypical features have been associated with both BD and Binge Eating Disorder (BED) (Angst et al., 2002). Moreover cyclothymic mood instability in patients with BED has been associated with severity of binge, poorer prognosis of obesity and reduced response to therapies (Fagiolini et al., 2003; Greenberg and Harvey, 1987). Comorbidity with multiple anxiety disorders (Akiskal et al., 2006; Perugi et al., 2003), alcohol and substance abuse (Maremmani et al., 2008, 2006) and impulse control disorder (Perugi and Akiskal, 2002) have been also more commonly observed in bipolar than unipolar MDE patients.

The possibility that denial and lack of insight, associated with manic and hypomanic phases, may represent mediating mechanisms between bipolarity and obesity can not be supported by our findings. Most of the depressive Obese patients in our study did not report long lasting severe manic phases, but short hypomanic episodes and lifetime hypomanic symptoms. Most of them showed various degree of discomfort with a full insight of the risks for health connected with obesity and related metabolic disorders. The major problem is that they cannot maintain long-term control on food intake and, in a certain sense, can be considered food addict. Hypomanic symptoms and mood instability may represent the background of the impulsive-addictive behaviors frequently observed in bipolar spectrum patients.

A great body of literature supports the hypothesis that substance abuse and pathological over-eating may be the phenotypic expression of a competing brain reward system (McIntyre et al., 2007; Volkow and Wise, 2005). This hypothesis is also supported by the high rates of cyclothymic temperament found in Obese patients (Alciati et al., 2007; Amann et al., 2009) suggesting that cyclothymic temperament and related hypomanic symptoms, sensation seeking and self-stimulating behavior might involve any type of potentially addictive substance or activity, such as food, alcohol, drugs, sex, gambling, shopping, etc. (Perugi and Akiskal, 2002).

Our study presents several methodological caveats that should be taken into account for the correct interpretation of the results. The main limitation is that, given the naturalistic approach, pharmacological treatments and co-morbidity with other psychiatric disorders that might have affected the prevalence of obesity, such as anxiety and eating disorders, are not explored and accounted for in our analyses.

In conclusion, in our national sample of patients with MDE, obesity is associated with bipolar subtype and (hypo)manic symptoms. These findings suggest the possibility that the presence of obesity in patients with MDE might be considered as a sign of bipolarity. The association is particularly strong for the most severe forms of overweight suggesting a possible relationship between bipolar spectrum, addictive behaviors and severe obesity. Further longitudinal studies in clinical and non-clinical populations are necessary to better define the burden and the role of the association between obesity and bipolarity. Prospective studies are needed to determine whether higher levels of hypomania can lead in time to a high risk of binge eating and obesity in the general population. Future clinical studies should investigate whether treatment of MDD in Obese subjects with mood stabilizing agents lead to a better control of food intake through mood stabilization compared to antidepressant treatment. Hypomanic switches and mood instability should also be assessed during treatment with antidepressants in order to determine if they are more frequent in Obese patients than in other MDD subjects.

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Data collection were supported by Boehringer Ingelheim Italia. Boehringer Ingelheim Italia had no further role in the analysis and interpretation of the data, in the writing of the report and in the decision to submit the manuscript for publication.

Conflict of interest
This study did not involve any drug treatment or devices. The authors report no conflict of interest relevant to this work.

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