

Body mass index and plasma leptin in psychiatric suicide attempters

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Abstract

OBJECTIVES: To evaluate body mass index (BMI) and its correlate plasma leptin levels that have been associated with psychiatric morbidity and suicidal behaviour, in relation to clinical features in psychiatric patients after a suicide attempt.

METHODS: BMI and plasma leptin were assessed in 198 patients (66 males, age range of 21 to 80 years) who were admitted to the hospital after a suicide attempt, 98 with major depressive disorder, 28 with bipolar disorder, 30 with psychosis, and 42 with personality or adjustment disorder, compared to data of 134 healthy subjects, and evaluated in relation to gender, diagnosis, mode of attempt, and pharmacological treatment before attempt. The ratio leptin/BMI was used as a measure of adipocyte leptin secreting activity.

RESULTS: Drugs taken for treatment before attempt, among them atypical neuroleptics, were not associated either to BMI or to plasma leptin. The positive correlation between BMI and leptin was significant in all groups. Compared to same gender controls, significant differences were found only for female patients, namely higher BMI for patients with psychosis and patients with bipolar disorder, while leptin/BMI ratio was higher only in females with bipolar disorder.

CONCLUSION: BMI and plasma leptin in psychiatric suicide attempters are elevated in certain diagnostic groups in females, not related to previous pharmacologic treatment. The lack of a control group without a history of suicide attempts does not allow the attribution of enhanced leptin secreting activity found in female bipolar attempters specifically to suicidal behavior or to the disorder as a diagnostic entity.

INTRODUCTION

Epidemiologic data indicate an association of high body mass index (BMI) with psychiatric morbidity, mainly with depression, bipolar disorder, or schizophrenia (Simon *et al.* 2006; Wang *et al.* 2006; Maina *et al.* 2008; Gurpegui *et al.* 2012), diagno-

ses in which suicide risk is high. The link between high BMI and psychiatric morbidity seems to be reciprocal, with obesity to increase the risk of depression, and depression to be predictive of developing obesity (Luppino *et al.* 2010).

The possible relationship between BMI and suicidal behavior (suicide, suicide attempts and

suicide ideation) has been investigated in a number of studies (Perera *et al.* 2015). In some studies, increased BMI was associated with decreased risk for completed suicide for both men and women (Magnusson *et al.* 2006; Kaplan *et al.* 2007; Mukamal *et al.* 2007). Regarding suicide attempts, epidemiological studies reveal gender differences in the association between BMI and risk for attempts, with women with elevated BMI to report more suicide attempts than women with normal BMI. On the contrary, in some studies an inverse relationship between BMI and suicide attempts was observed in males. Obese men were at lower risk to commit a suicide attempt compared to thinner men or to those with normal weight, while lower BMI was associated with increased risk of suicide attempts (Batty *et al.* 2010; Klinitzke *et al.* 2013; Zhang *et al.* 2013; Gao *et al.* 2013).

BMI is strongly positive correlated to plasma leptin levels, a hormone released primarily from white adipose tissue that regulates energy balance by suppressing food intake and stimulating energy expenditure via its action in the hypothalamus (Ostlund Jr *et al.* 1996; Jéquier 2002). Plasma leptin has been studied in psychiatric patients with depression, schizophrenia, bipolar disorder, and suicide attempters, with equivocal results (Deuschle *et al.* 1996; Kraus *et al.* 2001; Atmaca *et al.* 2002; Jow *et al.* 2006; Atmaca *et al.* 2008). The study of leptin in relation to suicidal behavior is of specific interest as it has been shown that leptin inhibits synthesis and release of serotonin by neurons in the brainstem (Finn *et al.* 2001; Yadav *et al.* 2011; Oury & Karsenty 2011), a neurotransmitter that has been connected with suicidal behavior (Träskman *et al.* 1981).

It is well established that certain psychotropic drugs may cause weight gain and influence plasma leptin levels (Hinze-Selch *et al.* 2000; Jin *et al.* 2008; Dent *et al.* 2012; Potvin *et al.* 2015). These considerations have to be taken into account in studies of associations of BMI and leptin with suicidal behavior in psychiatric patients.

In this study we searched for differences in BMI and plasma leptin between psychiatric patients after a recent suicide attempt and healthy control subjects. In attempters, we searched for possible associations with gender, diagnosis, mode of attempt (violent – non-violent attempt), and drugs taken for treatment before attempt.

MATERIAL AND METHODS

One hundred ninety four patients (62 males, 132 females) in the age range of 21 to 80 years who were admitted to the Psychiatric Clinic of “Attikon” General Hospital in Athens after a suicide attempt were included in the study. The suicide attempt was defined as “every self-directed injurious act with at least some intent to end one’s own life” (Mann 2003). Suicide intent was evaluated using the Suicide Intent Scale (Beck *et al.* 1974). Suicide attempts were characterized violent or

non-violent according to the criteria of Träskman *et al.* (1981).

Psychiatric diagnoses were established according to DSM-5. Ninety eight subjects suffered from major depressive disorder (MDD), 28 from bipolar disorder, 30 from psychosis, and 42 from personality disorder or adjustment disorder, assigned as ‘other diagnosis’ for statistical evaluation. Weight and height were measured with participants wearing light clothes and without shoes. BMI was calculated as weight in kilograms divided by height in meters squared. Leptin was estimated in plasma using the coated tube radioimmunoassay kit of DIAsource ImmunoAssays SA, Belgium. The manufacturer gives an analytical sensitivity of 0.1 ng/ml, and intra- and inter-assay sensitivities close to 5%. We calculated an intra-assay coefficient of variation of $4.8 \pm 3.8\%$.

Leptin levels were normalized to BMI by calculating the leptin/BMI ratio, which can serve as a measure of adipocyte leptin synthesis and release. Analyses were performed separately for males and females, as leptin levels are higher in females (Ostlund Jr *et al.* 1996).

For comparison we used a control group of 75 male and 90 female subjects in the same age range, with no history of suicide attempt or psychiatric illness.

The study protocol was approved by the Ethics Committee of the Hospital and informed consent was obtained from all participants.

For statistical evaluation, analysis of variance (ANCOVA) with age as covariate was used for comparisons of BMI and L/BMI ratio between suicide attempters and same gender healthy controls. Compared to controls were also subgroups of patients according to psychiatric diagnosis, and subgroups of patients who used violent or non-violent mode of attempt. Age was used as covariate in evaluating differences between groups, as metabolism decreases with ageing, leading potentially to increased body weight and to changes in BMI (St-Onge & Gallagher 2010; Fukagawa *et al.* 1990). Also, osteoporosis, which is related to age, is expected to reduce height (Knopp-Sihota *et al.* 2012) and thus influence BMI values.

Possible influence of previous drug therapy on BMI values or on plasma leptin levels was assessed by multiple regression analysis with dependent variable BMI or leptin, and independent variables drug(s) taken for treatment before attempt.

RESULTS

The score in Suicide Intent Scale was for male patients 14.1 ± 5.4 (range 3–24) and 13.4 ± 6.2 (range 1–26) for females. There were no associations of SIS score with BMI or L/BMI ratio in any group.

Table 1 shows the results of multiple regression analyses for male and for female patients in evaluation of possible influence of drugs taken for treatment before attempt on BMI or plasma leptin. Drug

Tab. 1. Multiple regression analyses with dependent variable Body Mass Index or plasma leptin levels, and independent variables drug(s) taken for treatment before attempt. The number of male and female patients on each drug category is also given (N).

	Males, n=66			Females, n=132		
		BMI	Leptin		BMI	Leptin
R		0.3392	0.3188		0.2174	0.2348
F		1.08	0.94		0.88	1.03
p		0.39	0.48		0.52	0.41
Drug category	N	beta/p-value	beta/p-value	N	beta/p-value	beta/p-value
None	23	-0.049/0.78	-0.084/0.64	34	-0.020/0.88	-0.063/0.64
Antidepressants	24	-0.102/0.51	-0.062/0.69	78	-0.086/0.49	0.023/0.85
Neuroleptics, typical	6	0.192/0.19	0.087/0.55	11	0.001/0.99	0.061/0.50
Neuroleptics, atypical	23	-0.058/0.68	-0.049/0.73	40	0.129/0.18	0.129/0.18
Benzodiazepines	25	-0.014/0.92	0.275/0.08	59	0.096/0.36	-0.015/0.89
Anticonvulsants	13	0.101/0.54	0.201/0.23	30	0.112/0.34	-0.019/0.87
Other drug(s)	19	0.179/0.37	-0.066/0.74	51	0.028/0.82	0.129/0.30

Tab. 2. Age, Body Mass Index and leptin/BMI ratio of controls and psychiatric patients after a suicide attempt.

	Males					Females						
	N	Age	BMI	L/BMI		N	Age	BMI	L/BMI			
All												
Controls	64	49.6±8.5	26.8±3.1	Ref	0.211±0.084	Ref	70	43.4±10.3	24.6±3.2	Ref	0.467±0.240	Ref
Attempt	66	52.5±16.3	27.0±4.2	0.81	0.220±0.103	0.67	132	44.5±14.2	26.6±5.7	0.012	0.536±0.380	0.19
Subsample												
Diagnosis												
MDD	30	56.9±16.7	26.3±3.9	0.54	0.236±0.112	0.30	68	47.6±14.1	25.6±4.9	0.39	0.534±0.370	0.28
BPD	7	46.4±7.8	29.2±4.7	0.06	0.235±0.113	0.44	21	47.6±9.7	30.2±6.7	0.001	0.708±0.402	0.001
Psychosis	14	45.1±12.0	26.8±4.9	0.97	0.214±0.079	0.77	16	37.6±10.3	28.1±6.2	0.049	0.478±0.318	0.81
Other	15	53.2±19.5	27.5±3.8	0.40	0.187±0.100	0.32	27	38.3±16.7	25.3±5.4	0.92	0.440±0.397	0.39
Mode of Attempt												
Non-violent	34	53.9±15.1	27.3±3.9	0.52	0.237±0.106	0.27	92	43.8±13.4	26.1±5.8	0.07	0.532±0.382	0.22
Violent	32	50.9±17.6	26.7±4.5	0.52	0.203±0.098	0.65	40	46.1±16.0	27.7±5.3	0.001	0.543±0.381	0.24

p-values of comparisons between patient groups and reference group (same gender controls) are given (ANOVA with age as covariate). MDD: major depressive disorder; BPD: bipolar disorder.

categories inserted in the model were: none, antidepressives, typical neuroleptics, atypical neuroleptics, benzodiazepines, anticonvulsants, and other drugs. No significant association with any drug category was found either for males or for females. Thus, treatment with atypical neuroleptics or antidepressives had no impact on BMI or on plasma leptin levels in the patient sample of the present study.

Plasma leptin levels in controls and attempters were 5.82±2.86 and 6.10±3.37 for males, and 11.9±6.9 and 15.5±13.3 ng/ml for females. Data for L/BMI are given in Table 2. The differences between genders were highly

significant ($p < 0.001$) for both controls and patients groups for leptin as well as for L/BMI ratio.

Age, BMI, and L/BMI ratio of male and female control subjects and patients are shown in Table 2. Data are also given for subgroups according to diagnosis and mode of attempt. The results of statistical analysis (p -values), when BMI or L/BMI of groups and subgroups of patients were compared to same gender control subjects are also given.

No significant differences were found for male attempters, either for the whole group or subgroups. The small subgroup of seven male patients with bipolar

disorder tended to show higher BMI values than controls (BMI 29.2 ± 4.7 compared to 26.8 ± 3.1 for male controls, $p=0.06$). This is worth mentioning, because the same result was found for female bipolar patients.

For females, BMI was significantly higher for the whole group of attempters ($p=0.012$), for patients with bipolar disorder ($p=0.001$) and for patients with psychosis ($p=0.049$). Significantly higher BMI values were also found for female subgroup with violent attempt compared to female controls, while the difference in BMI between violent and non-violent attempt was near significance ($p=0.07$).

Plasma leptin levels paralleled BMI values, and the positive correlation to BMI was present in all groups and subgroups of Table 2, except the small subgroup of seven male bipolar attempters. Regarding L/BMI ratio, the only significant difference was found for the subgroup of female attempters with bipolar disorder compared to female controls ($p=0.001$).

The finding of higher BMI in female patients with bipolar disorder and with psychosis led us to search for possible influence of treatment with atypical neuroleptics before attempt on BMI and leptin in these two subgroups. Twenty one from 37 female patients of these two diagnostic categories were taking atypical neuroleptics (mainly quetiapine or olanzapine). Comparisons between the groups with and without atypical antipsychotics showed no significant differences in BMI, plasma leptin levels, or L/BMI ratio (Table 3).

DISCUSSION

Body Mass Index in psychiatric patients with a recent suicide attempt was found significantly higher compared to same gender healthy controls for the whole group of female patients, in agreement with previous studies (Carpenter *et al.* 2000; Brunner *et al.* 2006; Dong *et al.* 2006). BMI of male psychiatric patients after a recent suicide attempt did not differ significantly compared to healthy control subjects.

Further analysis according to diagnostic subgroups showed that BMI in females was higher compared to healthy control subjects in attempters with bipolar disorder, but not in attempters with MDD. Similar were the results for males, although the number of male patients

with bipolar disorder in our sample is small, and the difference marginally significant. It has been previously reported that in patients with bipolar disorder, higher BMI correlated significantly with a history of suicide attempts (Wang *et al.* 2006; Fagiolini *et al.* 2004). BMI was assessed in the study of Kamali *et al.* (2012) in 139 bipolar patients, 48 males and 81 females, and was found increased compared to same male/female ratio healthy controls. Within the group, patients with a past history of suicidal behavior had significantly higher BMI than patients without a history of suicidal behavior (30.9 ± 6.4 versus 28.0 ± 4.5 , $p=0.003$). Similarly, bipolar patients with obesity were more likely to report a lifetime suicide attempt than patients without obesity (Goldstein *et al.* 2013).

The finding that BMI is higher in female patients with bipolar disorder but not in the subgroup of patients with depression, may explain contradictory results of previous studies where both diagnoses are grouped as patients with mood disorder. Higher BMI may be found when the number of patients with bipolar disorder in the study group is high, but not if the number is low.

Atypical antipsychotics have been implicated in weight gain (Jin *et al.* 2008; Dent *et al.* 2012; Teff & Kim 2011; Gebhardt *et al.* 2009). Most patients in our sample were on drug treatment before attempt, and 40 females and 23 males were taken atypical antipsychotics. Possible influence of treatment on BMI was evaluated by multiple regression analysis, with negative results (Table 1). Furthermore, comparisons between patients with and without atypical antipsychotics in the two groups of females with bipolar disorder or psychosis, in which higher BMI was found, showed no significant differences in BMI, plasma leptin levels, or L/BMI ratio (Table 3). It seems that the increased BMI found for female subgroups cannot be attributed to the drug therapy before attempt. Related to this finding are the results of the study of Maina *et al.* (2008), where higher BMI values were found in a group of 76 (43 females) drug-naïve bipolar patients compared with patients with obsessive-compulsive disorder, indicating that elevated BMI characterizes subjects with the disorder and is not due to drug treatment. High BMI in attempters of the present study cannot be attributed necessarily to suicidal behavior, as we have not data from a control group of patients, matched for gender and diagnosis, without a history of suicide attempts. This remains to be investigated in future studies.

Most studies have reported an inverse relationship between BMI and completed suicide (Klinitzke *et al.* 2013), and differences in biological markers have been suggested between attempters who use violent or non-violent methods, since violent suicide attempts are nearest to completed suicide (Ernst *et al.* 2009). In the present study, higher BMI values were found only for the subgroup of females with violent mode of attempt. No differences were found for females with non-violent attempt or males with either mode of attempt.

Tab. 3. Age, Body Mass Index, plasma leptin levels, and leptin/BMI ratio off male patients with bipolar disorder or with psychosis, with or without atypical neuroleptics (ATNRL) in their drug regime before suicide attempt. Evaluation by ANOVA with age as covariate.

Treatment	N	Age	BMI	Leptin	L/BMI
ATNRL-NO	16	44.9±9.8	28.3±4.7	18.7±14.1	0.623±0.415
ATNRL-YES	21	42.6±11.5	30.0±7.6	19.8±13.6	0.598±0.364
F (1, 34)			0.10	0.06	0.02
p-value			0.75	0.81	0.89

The known positive correlation of plasma leptin levels to BMI was present in the groups of patients of the present study, so differences in leptin levels between groups paralleled these for BMI. When the corrected to BMI leptin, i.e. the ratio leptin/BMI calculated for each subject, was used in evaluating leptin between groups, enhanced leptin/BMI values were found only for the subgroup of female bipolar attempters compared to controls. This variable, which expresses more adequately adipocyte leptin synthesis and release activity, has been used in a number of previous studies of leptin in other topics, but not in studies of leptin in relation to psychiatric patients with or without suicidal behaviour, where most studies use BMI as covariate in analysis of variance comparing leptin levels between groups.

There is no study where leptin levels were compared only in female bipolar patients with and without a history of suicide attempt. Barbosa *et al.* (2012) reported increased plasma leptin levels in a group of 30 patients of both genders with bipolar disorder in euthymic state, on drug treatment, compared to age, gender, and BMI matched healthy control subjects. In the study of Lee *et al.* (2014), depressed bipolar patients of both genders had higher leptin levels than euthymic patients, adjusted for age, gender, and BMI. No differences in serum leptin levels were reported in the study of da Graca Cantarelli *et al.* (2015), where bipolar patients and patients with major depressive disorder of both genders with and without suicide attempt were compared.

The results regarding leptin levels in depressed patients, not in relation to suicide attempts, are also ambiguous. Deuschle *et al.* (1996) found no differences between depressed patients and healthy controls, Esel *et al.* (2005) higher leptin levels in patients with depression, Pasco *et al.* (2008) higher leptin levels in women with a lifetime history of depression compared to women with no history of depression, and Kraus *et al.* (2001) lower levels both in male and female depressive patients.

The finding of enhanced leptin synthesis and release in bipolar female attempters compared to healthy controls cannot be attributed at present necessarily to suicidal behaviour. For this, data for a sex, diagnosis, age, and eventually duration of illness and drug treatment matched patient group without suicidal behaviour have to be obtained, and this, a limitation of the present study, remains to be done in the future. Nevertheless, the finding allows the hypothesis that increased leptin synthesis and release may inhibit central serotonergic activity in this group of patients, and may help in identifying another factor associated with suicidal behaviour in this group of patients.

In a recent meta-analysis of 101 reports from 22 countries (Tondo *et al.* 2016), attempt risk in bipolar disorder averaged 31.1% of subjects, with women to show a greater rate (33.7%) than men (25.5%). The identification of risk factors is important for suicide prevention and is expected to lead to improved inter-

ventions and specific treatment strategies (Schaffer *et al.* 2015).

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