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Serum leptin and cholesterol levels in schizophrenic patients with and without suicide attempts

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Objective: Previous studies demonstrate a relationship between lipid metabolism and suicide or impulsive–aggressive behaviours. Leptin seems to be related with lipid metabolism. Therefore, the aim was to measure total serum cholesterol and leptin levels in 16 medication-free schizophrenic patients with and without suicide attempts and in 16 healthy controls.
Method: Subjects were assessed by using Impulsivity Rating (IRS) and Modified Overt Aggression Scale (MOAS).
Results: The patients had lower total cholesterol and leptin levels in serum compared with the controls. Significantly lower total cholesterol and leptin levels were observed in patients who had attempted suicide compared with those who had not. The levels were observed to be low in violent attempters when compared with non-violent attempters. MOAS and IRS scores were negatively correlated with both cholesterol or leptin levels in patients.
Conclusion: The results indicated that medication-free schizophrenic patients have statistically significant lower serum cholesterol and leptin levels compared with controls and the difference is obvious in suicide attempters compared with non-suicide attempters and in violent attempters than non-violent attempters.

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Introduction

Earlier studies provide evidence that low cholesterol values are associated with psychiatric disorders related impulsive–aggressive and suicidal behaviours, e.g. antisocial personality disorder and schizophrenia (1–3). However, epidemiological and clinical studies yielded conflicting results concerning a supposed association between increased risk for suicide and violence and low serum cholesterol levels. Modai et al. (4) indicated no influence of cholesterol on serotonin uptake, as opposed to some investigators who suggested that high risk of suicide and aggressiveness in hypocholesterolemic individuals could be related to impaired serotonin transport (2, 3). Until now, no enough data has been available for schizophrenia itself, a disorder with a well-known increased risk of violence. In a study by Steinert et al. (5), no correlation between serum cholesterol levels and measures of violence in patients with schizophrenia and non-psychotic disorders was reported. In a retrospective study, it has been reported that although schizophrenic patients with physical violence had lower serum cholesterol levels, despite being statistically insignificant, than those without physical violence, there was no statistically significant difference between those with and without suicide attempts (6). Leptin, an adipocyte hormone, the product of the *ob* gene, has recently attracted considerable interest in psychiatric disorders (7–10). Leptin affects the intracellular lipid concentration via the decrease in synthesis of fatty acids and seems to be strongly related with lipid metabolism (11). However, as far as it is known, there is no data on leptin levels in schizophrenic patients with suicide attempt and aggressive–impulsive behaviours.

Aims of the study

To cross-sectionally measure serum total cholesterol and leptin levels in medication-free schizophrenic patients with and without suicide attempts and to examine a relationship with impulsivity, aggression, and violence.

Material and methods

The study consisted of 16 schizophrenic patients with suicide attempts (range 20–47 years) who were consecutively admitted into the emergency unit and age- and sex-matched with those without suicide attempts ($n = 16$, range 22–50 years) who were consecutively admitted into the Department of Psychiatry of our clinic. The patients without suicide attempts had no history of earlier suicide attempts. A DSM-IV diagnosis of schizophrenia was established on the basis of independent structured interviews (Structured Clinical Interview for DSM-IV; SCID) (12, 13) by two qualified psychiatrists. The patients with any kind of axis I comorbidity were excluded. In fact, 22 patients with suicide attempt applied during the study period, but six were excluded from the study. Three had taken psychotropic drugs within the previous 2 weeks, two had serious medical illness (diabetes mellitus and systemic lupus erythematosus) and one had a current history of cholesterol-lowering treatment.

Age and sex-matched 16 healthy staff members were included in the control group. They were all free of psychotropic medication and had no history of psychiatric disorder or suicide attempts.

Exclusion criteria for patients and controls included the presence of a severe physical illness, a history of alcohol and substance abuse or dependence, a previous history of cholesterol-lowering treatment, the presence of any endocrinological state and treatment with any medication within the previous 2 weeks. Nine patients had never taken psychopharmacological drugs (five patients from suicidal group and four from non-suicidal group). The other 23 patients had received the following drug treatments; classical antipsychotics (in 10 patients), olanzapine (in six patients), risperidone (in four patients), and quetiapine (in three patients), but had been without medication for 15 days (only one patient receiving quetiapine) to 4 years. Also, all of them had a history of prior treatments with various antipsychotics; classical neuroleptics (in 16 patients), depot neuroleptic (in eight patients), clozapine (in four patients), olanzapine (in two patients), and risperidone (in one patient).

All participants were carefully assessed to exclude any autoimmune, pulmonary, infectious diseases or neoplasms. All subjects were evaluated by a semi-structured questionnaire form which was designed by the authors in accordance with clinical experience and available information sources. All subjects were assessed by using Impulsivity Rating Scale (IRS) (14) and Modified Overt Aggression Scale (MOAS) (15). In addition, body mass index (BMI) was calculated by dividing the weight (in kilograms) by the squared height (in meters) (kg/m^2). All subjects gave fully informed written consent to take part in this study, which had Local Ethics Committee approval for the Firat University School of Medicine.

According to the criteria of Traskman et al. (16), suicide attempters were divided into two subgroups: violent ($n = 9$, knife wound in four patients, jumping from a high place in three patients, and firearm in two patients) and non-violent ($n = 7$, benzodiazepine ingestion in six patients and antibiotic ingestion in one).

The patients and controls fasted overnight. Venous blood samples were drawn from the antecubital vein at 08.00 hours to determine the serum levels of leptin and cholesterol. The leptin levels were measured with the DRG human leptin kit (DRG International, Inc., NJ, USA) by means of enzyme-linked immunoassay method. Total cholesterol levels were assayed using a Randox cromlin, total cholesterol kit (Randox laboratories Ltd, Cromlin, UK) and an Olympus AU 600 autoanalyzer (Olympus Corp., Tokyo, Japan).

Statistical analysis was performed by statistical package for social sciences (SPSS/PC 9.05 version, 1998, Chicago, IL, USA). Kruskal–Wallis analysis of variance (ANOVA) with correction according to the Bonferroni procedure for all *post hoc* comparisons was used. Chi-square (χ^2) test was used to compare categorical variables. Gender mean differences were examined by means of Mann–Whitney *U*-test. The general linear model command of the SPSS was used when controlling for covariates. Correlation analysis was performed by Pearson's and Spearman's rank correlations test, whenever appropriate. Differences were considered significant at $P < 0.05$ for all these tests.

Results

General characteristics of the patients and controls are summarized in Table 1. Patients with and without suicide attempts and healthy controls did not differ with respect to the age, sex ratio, length of illness, and BMI. Of the patients with suicide attempts, nine (56.3%) were violent and seven

Table 1. The mean leptin and cholesterol levels and some characteristics of the patients and controls

	I Schizophrenic patients with suicide attempts ($n = 16$)	II Schizophrenic patients without suicide attempts ($n = 16$)	III Controls ($n = 16$)	P
Age (years)	28.2 ± 5.1	30.1 ± 3.6	29.4 ± 3.2	$P > 0.05$
Sex (F/M)	9/7	8/8	8/8	$P > 0.05$
Duration of illness (years)	5.6 ± 3.3	6.1 ± 3.6	–	$P > 0.05$
BMI and biochemical parameters				
BMI (kg/m^2)	24.4 ± 2.4 (20–28)	23.9 ± 3.1 (22–27)	24.0 ± 3.4 (20–27)	$P > 0.05$
F	22.8 ± 2.8 (20–24)	22.7 ± 2.8 (22–25)	23.4 ± 2.4 (20–24)	$P > 0.05$
M	27.4 ± 2.5 (24–28)	24.1 ± 3.3 (23–27)	25.3 ± 3.7 (22–27)	$P < 0.05$ I–II
P	< 0.05	> 0.05	> 0.05	
Total cholesterol (mg/dl)	136.6 ± 18.2 (117.4–156.7)	167.6 ± 21.7 (130.3–208.9)	190.3 ± 26.8 (160.5–218.6)	$P < 0.01$I–II $P < 0.05$ II–III $P < 0.001$ I–III
F	132.7 ± 13.5 (117.4–145.9)	161.5 ± 19.6 (130.3–186.5)	184.1 ± 17.9 (160.5–207.7)	$P < 0.05$II–III $P < 0.01$ I–II, I–III
M	139.3 ± 25.2 (126.5–161.7)	171.6 ± 23.5 (155.7–208.9)	195.3 ± 26.8 (170.5–218.6)	$P < 0.05$II–III $P < 0.01$ I–II, I–III
P	> 0.05	> 0.05	> 0.05	
Leptin (ng/ml)	5.1 ± 3.6 (1.8–10.5)	7.3 ± 4.7 (2.4–13.5)	13.5 ± 5.2 (2.9– 16.1)	$P < 0.05$ I–II $P < 0.001$ I–III,II–III
F	6.7 ± 3.9 (2.8–10.5)	8.8 ± 3.9 (3.1–13.5)	14.9 ± 5.1 (3.4–16.1)	$P < 0.05$ I–II $P < 0.01$ I–III, II–III
M	4.5 ± 3.6 (1.8–7.1)	7.1 ± 3.1 (2.4–10.1)	12.6 ± 4.2 (2.9–5.2)	$P < 0.05$ I–II $P < 0.01$ I–III, II–III
P	< 0.05	> 0.05	< 0.05	

F, female; M, male; BMI, body mass index.

(43.7%) were non-violent suicide attempters. There was a predominance of residual schizophrenia in both groups. Clinical subtypes were as follows: paranoid in five patients from the suicidal group and in four patients from non-suicidal group; disorganized in two patients from suicidal group and in two patients from non-suicidal group; undifferentiated in two patients from suicidal group and in one patient from non-suicidal group and residual schizophrenia in seven patients from suicidal group and nine patients from non-suicidal group.

The mean cholesterol levels for patients with and without suicide attempts, and controls were 136.6 ± 18.2 (range 117.4–156.7), 167.6 ± 21.7 (range 130.3–208.9) and 190.3 ± 26.8 (range 160.5–218.6) mg/dl, respectively ($P < 0.01$ for patients with vs. without suicide attempts, $P < 0.05$ for those without suicide attempts vs. controls, and $P < 0.001$ for those with suicide attempts vs. controls). Additionally, there was considerable difference between violent and non-violent suicide attempters ($P < 0.05$). Significant difference in mean serum cholesterol levels among groups was found after controlling for BMI or age ($F = 4.71$, $P < 0.05$ adjusted for BMI; $F = 4.17$, $P < 0.05$ adjusted for age). In addition, when comparing the mean cholesterol level between sexes within each group, no statistically significant difference was observed ($P > 0.05$).

The mean leptin levels for patients with and without suicide attempts, and controls were 5.1 ± 3.6 (range 1.8–10.5), 7.3 ± 4.7 (range 2.4–13.5) and 13.5 ± 5.2 (range 2.9–16.1) ng/ml, respectively ($P < 0.05$ for patients with vs. without suicide attempts, $P < 0.001$ for those without suicide attempts vs. controls, and $P < 0.001$ for those with suicide attempts vs. controls). Additionally, there was a considerable difference between violent and non-violent suicide attempters ($P < 0.05$). Significant difference in mean leptin levels among groups was found after controlling for BMI or sex ($F = 14.23$, $P < 0.001$ adjusted for BMI; $F = 4.84$, $P < 0.05$ adjusted for sex). In addition, when comparing the mean leptin level between sexes within each group, statistically significant difference was found in patients with suicide attempts and healthy controls ($P < 0.05$) but not in those without suicide attempts ($P > 0.05$).

Total cholesterol and leptin levels in groups were presented as boxplot in Figs 1 and 2.

There was a positive correlation between cholesterol and leptin levels in patients with and without suicide attempts ($r = 0.56$, $P < 0.05$; $r = 0.58$, $P < 0.05$, respectively), but not in controls ($r = 0.12$, $P > 0.05$). The leptin levels were correlated with the BMI in suicide attempters ($r = 0.82$, $P < 0.01$) and non-suicide attempters ($r = 0.63$, $P < 0.05$), whereas there was a

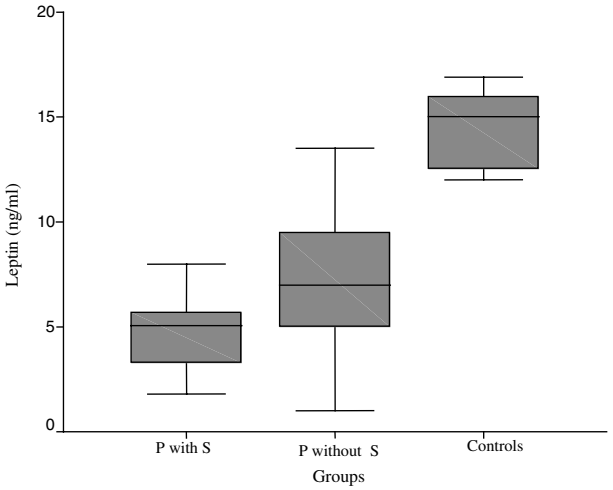

Fig. 1. Leptin levels of groups as boxplot.

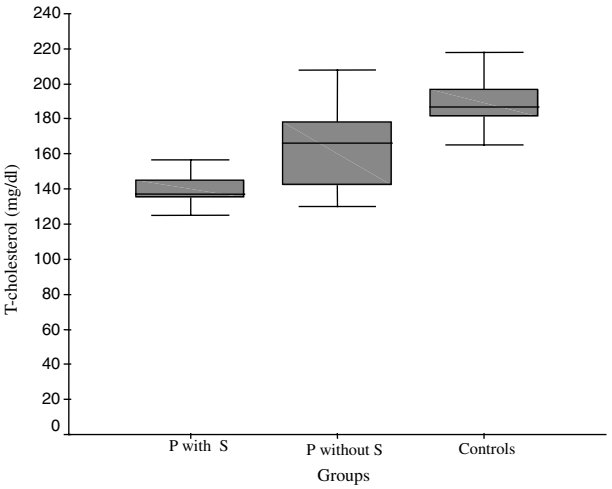

Fig. 2. Total cholesterol levels of groups as boxplot.

tendency toward such a correlation in controls ($r = 0.42$, $P > 0.05$). In addition, cholesterol levels were correlated with the BMI in all groups ($r = 0.61$, $P < 0.05$ for suicidal patients; $r = 0.58$, $P < 0.05$) for non-suicidal patients and $r = 0.66$, $P < 0.05$ for controls). In the patient group, there was an inverse correlation between total cholesterol levels and MOAS ($r = -0.80$, $P < 0.01$ for violent; $r = -0.64$, $P < 0.05$ for non-violent suicide attempters and $r = -0.58$, $P < 0.05$ for non-suicidal patients) or IRS ($r = -0.76$, $P < 0.01$ for violent; $r = -0.58$, $P < 0.05$ for non-violent suicide attempters and $r = -0.54$, $P < 0.05$ for non-suicidal patients). Moreover, the leptin levels were negatively correlated with MOAS in violent and non-violent suicide attempters but not in non-suicidal patients ($r = -0.66$, $P < 0.05$ for violent; $r = -0.62$, $P < 0.05$ for non-violent suicide attempters and $r = 0.18$, $P > 0.05$ for non-suicidal patients) or IRS ($r = -0.56$, $P < 0.05$ for violent; $r = -0.53$, $P < 0.05$ for non-violent suicide attempters and $r = -0.54$, $P < 0.05$ for non-suicidal patients) (Table 2).

Discussion

This study demonstrates that medication-free schizophrenic patients have lower total serum cholesterol and leptin levels compared with healthy controls and patients with suicide attempts than those without suicide attempts. Moreover, significantly lower total cholesterol and leptin levels have been found in violent than non-violent suicide attempters. In the patient group, both total serum cholesterol and leptin levels were negatively correlated with impulsivity and impulsive aggression, as determined by the IRS and MOAS.

Huang and Wu (6) reported that schizophrenic patients with physical violence had lower serum cholesterol levels, despite not being statistically significant, than those without physical violence. In the previous study (17), 24 suicide attempters (four schizophrenic patients) and 24 healthy controls were compared for total serum cholesterol and leptin levels. It is to be noted that there has been no overlap with the sample from the present study. In the previous study, the patients with suicide

Table 2. Correlations between cholesterol values, leptin values, age, and scale scores in all groups

	P with S				P without S		Control group	
	Violent		Non-violent					
	C	L	C	L	C	L	C	L
C	–	0.58*	–	0.53*	–	0.58*	–	n.c.
L	0.58*	–	0.53*	–	0.58*	–	n.c.	–
BMI	0.63*	0.8**	0.60*	0.80**	0.58*	0.63*	0.66*	n.c.
MOAS	−0.80**	−0.66*	−0.64*	−0.62*	−0.58*	n.c.	–	–
IRS	−0.76**	−0.56*	−0.58*	−0.53*	−0.54*	n.c.	–	–

C, cholesterol; L, leptin; P, patients; S, suicide; BMI, body mass index; MOAS, Modified Overt Aggression Scale; IRS, Irritability Rating Scale.
* $P < 0.01$, ** $P < 0.05$ n.c., no correlation.

attempts had significantly lower serum cholesterol and leptin levels than controls, irrespective of psychiatric diagnoses, and it was suggested that suicide attempts seemed to be associated with lower serum cholesterol and leptin levels. Alvarez et al. (18) suggested that low serum cholesterol might be associated with the violence of suicide attempt and not with suicide attempt itself. In the present study, schizophrenic patients with violent suicide attempts had a markedly lower serum cholesterol and leptin levels compared to those with non-violent suicide attempts. Low leptin levels had been previously reported in patients with schizophrenia (10), as in this research. However, so far, leptin concentrations have not been investigated in schizophrenic patients with suicide attempts. It has been recently suggested that circulating leptin is derived not only from adipose tissue, but also from the brain (19) and so it may be speculated that decreased leptin levels may reflect the decreased leptin production from the brain. It has been shown to be an interaction between leptinergic and serotonergic systems in central nervous system and mentioned that leptin administration stimulated serotonin turnover (20). In addition, reduced serotonin activity has been implicated in impulsivity, aggressive, and suicidal behaviour (21). Kaplan et al. (22) reported decreased serum cholesterol levels and cerebrospinal fluid (CSF) concentrations of 5-hydroxy-indoleacetic acid in primates which were supplied with low fat diet. It has been suggested that reduced plasma cholesterol could suppress the cholesterol/phospholipid ratio in neuronal membranes with consequent alterations in membrane fluidity, viscosity, and function, including serotonin receptors and serotonergic neurotransmission (23). Moreover, phospholipase A_2 (PLA_2) and fatty acid coenzyme A ligase-4 (FACLs-4) are two key enzymes involved in signal transduction processes following the activation of various receptors, e.g. DA_2 and 5-HT_2, which are involved in the pathophysiology of schizophrenia and suicide attempts (24). In the previous study, low serum cholesterol and leptin levels had been found to be associated with all dimensions of borderline personality disorder which is characterized by aggressive behaviours, impulsivity, and suicide attempts but not related to the presence or the severity of depression (7). A positive correlation between serum leptin concentration and total cholesterol was determined and leptin affects the intracellular lipid concentration via decrease in synthesis of fatty acid and seems to be strongly related with lipid metabolism (11, 25), as supported by this study. Therefore, these relationships have allowed to consider that leptin may be associated with violent and non-violent suicide attempts, although, in suicide attempts, the exact roles of cholesterol, leptin and serotonin which seem to be related with each other is obscured by the dearth of investigations. Meanwhile, it should be noted that the suicidal behaviour in schizophrenia might be related to specific clinical characteristics of schizophrenia (e.g. hallucination, delusion) besides impulsivity and depressed mood. Amador et al. (26) found that awareness of the presence of delusions was related to increased suicidal behaviour in schizophrenia which is in accordance with the finding demonstrating that more than 10% of suicide attempters with schizophrenia reported that they made attempts because they are bothered by positive symptoms (27). Positive symptoms, negative symptoms, depression, substance abuse and loss of social support – all these increase the risk for suicidal behaviour in schizophrenia but only when there is an underlying vulnerability to self-directed violence. Low CSF homovanillic acid (HVA) has been found by some investigators in alcoholic, violent offenders and in suicide attempters (28); however, others do not find a correlation between CSF HVA and suicidal behaviour (29). Agren (30) reported a complex relationship between methoxy-hydroxy-phenylglycol (MHPG) and suicidal behaviour. As seen, there is a possible complex interactions among suicidal behaviour, serotonergic and dopaminergic systems in terms of suicide–psychosis relationship and this requires futher investigations. It has been reported that acute stress related to or even induced by the admission to a psychiatric unit may decrease leptin levels via elevated catecholamine release (31). However, prospective studies have suggested that leptin levels have partially remained stable (32, 33), consequently it is difficult to hypothesize that decreased levels is simlpy caused by acute stressful conditions. Meanwhile potential interactions of antipsychotics with leptin levels should be mentioned. In their unselected, naturalistic trial, Herran et al. (34) found that leptin levels in schizophrenic patients on chronic antipsychotic treatment did not differ between patients and controls and were correlated with weight gain, even after controlling for current weight, but did not show any association with clinical variables. However, in the previous study (32), it was suggested that leptin might be associated with quetiapine- and olanzapine-induced weight gain in accordance with the study by Herran et al. and proposed in contrast with their study that leptin could mediate the beneficial effects of antipsychotics.

The main limitations of the present study include the small sample size, and uncontrolled economical status and dietary differences which might affect

the total serum cholesterol and leptin levels and that no scale was used to assess the clinical severity of schizophrenia and no evaluation was carried out to establish a relationship between leptin and psychopathology. Apart from this, given the small sample size, the exclusion of six of 22 patients from the suicidal group might have downward-biased the cholesterol and leptin levels (e.g. the baseline levels were probably high atleast in the patient taking cholesterol-lowering treatment). In summary, the results suggested that medication-free schizophrenic patients may have lower total serum cholesterol and leptin levels compared with healthy controls and patients with suicide attempts than those without suicide attempts and that the difference seems to be more obvious in violent suicide attempters compared with non-violent suicide attempters, suggesting low serum cholesterol and leptin levels in schizophrenic patients are related to all dimensions of suicide attempts; suicidality, impulsive aggression and violence. Future studies should reveal in detail the longitudinal course of leptin and cholesterol levels in patients with and without suicide attempts.

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