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Serum Ghrelin and Cholesterol Values in Suicide Attempters

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Key Words
Ghrelin · Cholesterol · Suicide · Serotonin

Abstract
In our previous study, we demonstrated that suicide attempters had statistically significant lower leptin and cholesterol levels compared with healthy controls. In keeping with our previous report regarding lower serum cholesterol and leptin levels in suicide attempters compared with healthy controls, the relationship between cholesterol and leptin, and ghrelin, we aimed to evaluate serum total cholesterol and ghrelin levels in suicide attempters. In the present study, 30 patients with suicide attempts (aged 18–47 years) and the same number of healthy controls were compared with regard to serum total cholesterol and ghrelin levels. The mean cholesterol level of the patients was significantly lower than that of the controls. On the other hand, the suicide attempters had significantly higher ghrelin levels compared with the controls. The results suggest that suicide attempts seem to be associated with decreased serum cholesterol and higher ghrelin values.

Introduction

There have been numerous reports suggesting an association between low cholesterol levels and impulsive-aggressive behaviors [1] and suicide attempts [2]. However, epidemiological and clinical studies also yielded conflicting results concerning a supposed association between increased risk for suicide and violence, and low serum cholesterol levels. Modai et al. [3] 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 [4]. Ghrelin – an endogenous ligand for the growth hormone secretagogue receptor – is a novel 28-amino-acid peptide hormone [5]. It is secreted by various parts of the body, e.g. by the stomach [6], the kidneys [7] and the placenta [8]. In rats and mice, intracerebroventricular ghrelin stimulates food intake in a dose-dependent manner [9]. Intravenous ghrelin at 5.0 pmol kg^{-1} min^{-1} increases appetite and food intake in humans [10]. Furthermore, plasma ghrelin concentrations of humans correlate inversely with body adiposity [11]. The effects of ghrelin are partly mediated in the hypothalamus via neuropeptide Y (NPY) [12]. Ghrelin stimulates NPY production and can antagonize the inhibition of NPY expression caused by leptin administration. It is evident that the biological ef-

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fects of ghrelin as well as the regulation of plasma ghrelin levels during different states of acute and chronic energy balance appear to mirror effects and regulation of leptin. Ghrelin and leptin not only seem to have opposite effects at the exact same targets, such as the hypothalamic neuroendocrine network encircling the melanocortin receptors and NPY neurons, they are also primarily secreted at opposite ends of the energy balance spectrum. As glucocorticoids can prevent the fasting-induced decline in serum leptin, it was proposed that hypercortisolism in depression might counteract the reduction in leptin secretion caused by decreased food intake and weight loss [13]. Elevated serum leptin in depression might in turn further promote corticotrope releasing hormone (CRH) release, which plays a major role in behavioral responses to stressors, as shown in animals, and hence contribute to the hypothalamo-pituitary-adrenal (HPA) system hyperactivity seen in depression [14]. In mammals, intracerebroventricular (ICV) CRH injection inhibits food intake, leads to anxiety behavior and induces glucocorticoid release from the adrenal glands [15]. Moreover, ICV ghrelin injection elevates plasma adrenocorticotropine-releasing hormone and corticosterone concentrations [16]. These facts suggest that central ghrelin may interact with CRH, HPA axis and subsequently anxiety behavior. Although ghrelin might seem to be the counterpart of leptin [17], in light of the current data situation it should be pointed out that leptin is involved in the long-term modulation of energy homeostasis, whereas ghrelin seems to be implicated more specifically in meal initiation and/or termination, resulting in a short-term regulation of energy balance.

In our previous study, we demonstrated that suicide attempters have statistically significant lower leptin and cholesterol levels compared with healthy controls [18]. In keeping with our previous report regarding lower serum cholesterol and leptin levels in suicide attempters compared with healthy controls [14], the relationship between cholesterol and leptin, and ghrelin, we aimed to evaluate serum total cholesterol and ghrelin levels in suicide attempters.

Methods

Subjects and Clinical Evaluation

Thirty patients with suicide attempts (aged 18–47 years) who had consecutively applied to the Firat University School of Medicine Emergency Unit or directly to the Department of Psychiatry were included in the study. The detailed clinical evaluation was performed by 1 trained psychiatrist within 2 days after admission for all patients (4 patients in the general surgery unit, 12 in the emergency unit, 6 in the traumatology clinic, 2 in the plastic surgery clinic and 6 in our clinic after first intervention in the emergency unit). A trained investigator evaluated each patient by using the Structured Clinical Interview for DSM-IV (SCID-I) [19] and the Structured Clinical Interview for DSM-IV Personality Disorders (SCID-II) [20]. Thirty age- and gender-matched healthy staff members were included in the control group. The controls were interviewed with the nonpatient version of the SCID (SCID-NP) to exclude any axis I disorder. In addition, they were all free of psychotropic medication and had no history of psychiatric disorder. All subjects were administered the Hamilton Depression Rating Scale (HDRS) [21].

Exclusion criteria for both patients and controls included the presence of a severe physical illness, the history of alcohol and substance abuse or dependence without an abstinent period of minimally 4 weeks, previous history of cholesterol lowering treatment, the presence of any endocrinological state, treatment with any medication within the last 2 weeks and excessive obesity. All participants were carefully assessed to exclude autoimmune, pulmonary, infectious diseases and neoplasms. In addition, body weight and height as well as the body mass index (BMI = weight/height^2) were measured in the patients and controls. The study was approved by the local ethics committee, and all subjects gave written informed consent.

Blood Sampling and Biochemical Determination

To determine the serum levels of ghrelin and total cholesterol, venous blood samples were obtained at 08.00 a.m. after overnight fasting. In the patients, blood was collected within 24 h after the suicide attempt. The ghrelin levels were measured according to the manufacturer's instructions using a ghrelin radioimmunoassay kit (Phoenix Pharmaceuticals, Human Ghrelin RIA kit, Belmont, Calif., USA) [22]. The normal human serum level is 120–220 mg/dl for total cholesterol and 87.79 ± 10.27 pg/ml for ghrelin.

Statistical Analysis

Statistical analysis was performed by the Statistical Package For Social Sciences (SPSS/PC 9.05 version, 1998). The data were presented as means ± standard deviation (SD), and differences between the 2 groups were examined using Student's t test. The General Linear Model command of the SPSS was used when controlling for covariates. Relationships between variables were ascertained by means of Pearson's product moment correlation coefficients or through simple regression analyses. Differences at $p < 0.05$ were considered statistically significant.

Results

Suicide attempters and healthy controls did not differ with respect to age and sex ($p > 0.05$). Of the patients, 19 (63.3%) were violent suicide attempters (deep knife wound in 10 patients, jumping from a high place in 6 and firearm in 3), whereas 11 (36.7%) were nonviolent suicide attempters (benzodiazepine ingestion in 11 patients, vita-

Table 1. Participant characteristics

	Suicide attempters (n = 30)	Healthy controls (n = 30)	p value
Age range, years	27.9 ± 12.4	28.8 ± 15.3	>0.05
Sex ratio, F/M	18/12	20/10	>0.05
BMI	22.1 ± 2.8	23.3 ± 2.5	>0.05
HDRS	12.7 ± 4.2	6.8 ± 3.1	<0.05
Psychiatric diagnosis			
Major depressive disorder	13	–	
Schizophrenia	4	–	
Schizoaffective disorder	1	–	
Bipolar disorder	5	–	
Depressive state	3	–	
Manic state	2	–	
Personality disorder	7	–	
Total serum cholesterol, mg/dl	202.2 ± 28.6	152.3 ± 20.5	<0.05
Ghrelin, pg/ml	104.6 ± 20.9	158.2 ± 41.0	<0.001

The values are means ± SD. Differences between the 2 groups were examined using Student's t test.

min B1 capsules in 4 and analgesic ingestion in 1). The mean HDRS scores of the patients and controls were 12.7 ± 4.2 and 6.8 ± 3.1, respectively ($p < 0.05$). Table 1 shows the characteristics of all the study participants.

The serum cholesterol levels were decreased in 17 patients (56.7%) and 1 control (3.3%), when individually compared with normal cholesterol values adjusted for BMI and gender. The mean cholesterol levels for suicide attempters and controls were 152.3 ± 20.5 and 202.2 ± 28.6 mg/dl, respectively. The mean level of the patients was significantly lower than that of the controls ($p < 0.05$). In addition, when comparing the mean cholesterol level between the sexes within each group, no statistically significant difference was found ($p > 0.05$).

The ghrelin levels were increased in 19 (63.3%) suicide attempters and 2 (6.7%) controls, when individually compared with normal ghrelin levels adjusted for BMI and sex. The mean ghrelin levels for suicide attempters and controls were 158.2 ± 41.0 and 104.6 ± 20.9 pg/ml, respectively. A significant difference in mean ghrelin levels between the groups was found after controlling for BMI, sex and age ($p < 0.001$). When comparing the mean ghrelin level between the sexes within each group, no statistically significant difference was found ($p > 0.05$).

There was a negative correlation between the mean cholesterol and ghrelin levels both in suicide attempters and controls ($r = -0.56$, $p < 0.05$ for suicide attempters and $r = -0.58$, $p < 0.05$ for controls). Between total cholesterol levels and BMI, there was a positive correlation in all groups ($r = 0.56$, $p < 0.05$ for suicide attempters and $r = 0.50$, $p < 0.05$ for controls). The ghrelin levels negatively correlated with BMI in the suicide attempters ($r = -0.82$, $p < 0.01$), whereas there was no significant correlation in the controls ($r = -0.28$, $p > 0.05$). There was no correlation between HDRS and total cholesterol ($r = 0.20$, $p > 0.05$) or ghrelin levels ($r = 0.18$, $p > 0.05$). This statistical insignificance remained when the major depression group was examined alone ($r = 0.23$, $p > 0.05$).

Discussion

The present study is the first one evaluating serum ghrelin levels in suicide attempters and demonstrated that suicide attempters had higher serum ghrelin and lower cholesterol values compared with healthy controls. The studies carried out in psychiatric patients implicated an association between low cholesterol levels and suicide attempts [2]. However, some authors reported that this relation existed only in patients with violent suicide attempts [23]. Alvarez et al. [24] suggested that low serum cholesterol levels might reflect the dimensions of suicidality and violence rather than that of impulsivity. In our previous study, we demonstrated that suicide attempters have statistically significant lower leptin and cholesterol levels compared with healthy controls [18]. Kaplan et al. [25] reported low serum cholesterol levels and cerebrospinal fluid (CSF) concentrations of 5-hydroxyindolace-

tic acid in primates which were given low-fat diet and proposed that serum cholesterol could affect serotonin metabolism. Different hypothetic explanations have been reported to account for the association between cholesterol and aggression, violence or suicidal behaviors. 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 (5-HT) receptors and serotonergic neurotransmission [26]. Moreover, phospholipase A_2 and fatty acid coenzyme A ligase 4, which are involved in lipid metabolism, are 2 key enzymes involved in signal transduction processes following the activation of various receptors, e.g. 5-HT_2, which may be involved in the pathophysiology of both violence and suicide attempts [27]. Fasting ghrelin levels have been found to correlate most strongly with insulin and cholesterol levels [28], which has been supported by this study. On the other hand, Brunetti et al. [29] reported depolarization-stimulated serotonin release to be inhibited by ghrelin and not to be affected by amylin, emphasizing an interaction between ghrelin and serotonergic systems in the central nervous system. In addition, low serotonin activity has been implicated in impulsivity and suicidal behavior [30]. Suicidal patients often have experiences of stressful life events [31] as well as difficulties in coping with stress [32]. This in turn might cause disturbances in the stress system (e.g. the HPA axis) [33]. In mammals, ICV CRH injection inhibits food intake, leads to anxiety behavior and induces glucocorticoid release from the adrenal glands [15]. Moreover, ICV ghrelin injection elevates CRH, plasma adrenocorticotropine-releasing hormone and corticosterone concentrations [16]. These facts suggest that central ghrelin may interact with CRH, HPA axis and subsequently with anxiety behavior. Therefore, these relationships have allowed us to consider that ghrelin may be associated with suicide attempts, although, in suicide attempts, the exact roles of cholesterol, CRH, ghrelin and serotonin, which appear to be associated with each other, have been obscured by limited investigations done so far.

The main limitations of the present study include the small sample size, that we could not control economical status and dietary differences which might affect the serum total cholesterol and ghrelin levels, and that we did not differentiate between violent or nonviolent suicide attempters. It must be noted even in the Discussion that we are not aware of e.g. the effect of the menstrual cycle on the biological parameters studied. Among the limitations of the study, we should also mention the fact that our findings refer to a single morning determination of plasma ghrelin, in spite of the well-defined circadian rhythm of this peptide. Lastly, weight loss, which might be seen in depression or schizophrenia, and sleep disorders may both be associated with altered ghrelin levels [34–36] which were not taken into consideration.

In conclusion, this is the first report to investigate the concentrations of circulating ghrelin in patients with suicide attempts. The results suggest that suicide attempts seem to be associated with decreased serum cholesterol and ghrelin values. However, further studies with larger numbers of patients are required.

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