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Weight Gain and Serum Leptin Levels in Patients on Lithium Treatment

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Key Words
Leptin · Lithium · Weight · Serotonin

Abstract
Weight gain is a frequent adverse effect associated with lithium use. Leptin is an adipocyte hormone, regulating food intake and energy balance providing the hypothalamus with information on the amount of body fat. Therefore, we planned to evaluate whether lithium administration was associated with weight gain, and leptin levels. The study consisted of 15 consecutive inpatients with bipolar I disorder according to DSM-III-R. The fasting serum leptin levels were measured. The patients were evaluted at baseline and at the eighth week according to the body mass index, weight, Young Mania Rating (YMRS) and Hamilton Depression Rating (HAM-D) scales, and serum leptin levels. With respect to the leptin levels, a significant difference was observed after lithium treatment. There was a significant positive correlation between the changes in leptin levels and the duration of illness. The change in total YMRS scores correlated with change in leptin levels and that in weight. In conclusion, our result suggest that leptin may be associated with lithium-induced weight gain.

Introduction

Lithium (Li) carbonate is the first-line drug for the prophylaxis and treatment of bipolar disorders. Excessive weight gain related to long-term Li administration is frequently reported [1].

Leptin is an adipocyte hormone, as the product of the *ob* gene, regulating food intake and energy balance providing the hypothalamus with information on the amount of body fat [2]. The growing number of studies have focused on the leptin levels in the various psychiatric disorders recently [3–6]. Leptin administration has reduced food intake and weight [7, 8], suggesting its role on weight regulation. One of the physiologic roles of leptin is to limit food intake and leptin deficiency leads to hyperphagia. In contrary, it has also induced hypophagia when administered to lean mice [9]. It has been reported that leptin affects intracellular lipid concentration via a decrease in the synthesis of fatty acid and triglycerides and an increase in lipid oxidation [10]. The weight gain induced by atypical antipsychotics, clozapine and olanzapine, has been reported to be associated with an increase in the leptin levels [11]. In only one study, the effects of Li on leptin in healthy premenopausal women have been evaluated and it has been reported that leptin levels were not

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affected by Li [12]. To the best of our knowledge, there has been no study regarding the association between leptin and lithium use in a patient population. To explore the pathophysiology of weight gain on lithium treatment, we aimed to investigate changes in weight, body mass index (BMI), and leptin levels.

Method

The study consisted of 15 consecutive inpatients (9 females and 6 males; range 21–42 years) with bipolar I disorder, either manic episode or mixed episode, according to DSM-III-R with a minimum total score of 20 on the Young Mania Rating Scale (YMRS) [13] who applied to Firat University School of Medicine Department of Psychiatry. In fact, 19 patients were started on lithium treatment during the study period, but 4 were excluded from the study due to requirement of additional drug (n = 3; chlorpromazine use), and discontinuation because of intolerance (n = 1). The majority of the patients (73.3%) were experiencing a manic episode whereas the rest were experiencing a mixed episode (26.7%). All patients received lithium monotherapy. The only concomitant medication permitted was benzodiazepine. The mean daily dose of lithium was 1,147 mg/day (ranged from 900 to 1,500 mg).

The clinical evaluation was performed by a senior psychiatrist using Structured Interview for DSM-III-R (SCID) [14] within one day after admission for all patients. The patients with any kind of axis I comorbidity were excluded. All participants were free of all medications at least in the previous 2 weeks. Exclusion criteria included the presence of a severe physical illness, a history of alcohol and substance abuse or dependence, a previous history of lipid lowering treatment and the presence of any endocrinological state. All participants were carefully assessed to exclude any autoimmune, pulmonary and infectious disease, or neoplasms. All subjects were evaluated by a semi-structured questionnaire form which was arranged by authors in accordance with the clinical experience and available information sources. BMI was calculated dividing the weight (in kilograms) by the squared height (in meters) (BMI = kg/m^2). After the complete description of the study to the subjects, written informed consent was obtained from each patients, the study was approved by Local Ethics Committee of the Firat University School of Medicine.

All patients received a routine hospital diet. The patients were evaluated at baseline and at the eighth week with respect to the Hamilton Depression Rating Scale (HAM-D) [15], YMRS, BMI, weight, serum leptin levels.

The patients and controls fasted overnight. Venous blood samples were drawn from the antecubital vein at 08.00 a.m. to determine the serum levels of leptin and cholesterol. The leptin levels were measured with the Linco rat leptin kit (Linco Corp., St. Charles, Mo., USA) radioimmunoassay in an LKB Wallac Multigamma counter 1261 (Wallac Corp., Turku, Finland).

Statistical analysis was performed by using the statistical package for social sciences (SPSS/PC 9.05 version, 1998). The paired t test was used to compare the BMI, weight, total HAM-D and YMRS scores, and leptin levels before and after treatment. Correlation analysis was performed by Pearson's and Spearman Rank correlation test, whenever appropriate. Differences were considered significant at $p < 0.05$ for all these tests.

Table 1. General characteristics, scale scores, and leptin levels in patients before and after treatment

	Before treatment (n = 15)	After treatment (n = 15	p
Age, years	32.3 ± 5.3	–	–
Sex, female/male	8/7	–	–
Duration of illness, years	5.7 ± 3.7	–	–
BMI, kg/m^2	23.8 ± 1.9	26.8 ± 2.1	<0.05
Body weight, kg	65.2 ± 8.3	71.1 ± 6.5	<0.05
YMRS	24.8 ± 4.3	6.1 ± 2.3	<0.01
HAM-D	6.4 ± 1.6	6.8 ± 2.1	>0.05
Leptin, ng/ml	6.9 ± 3.1	10.3 ± 3.7	<0.05

Results

All patients completed the 6-week treatment period. The mean age and the duration of illness were 32.3 ± 5.3 and 5.7 ± 3.7 years, respectively. The mean weight and BMI gain since the onset of the study were statistically significant ($p < 0.05$), with no differences between sexes.

The leptin levels were decreased in 6 (40.0%) patients, when individually compared with normal leptin levels adjusted for BMI and gender. The mean increase in the leptin levels was 3.5 ± 2.2 ng/ml. A significant difference was observed after lithium treatment in the leptin levels ($p < 0.01$).

The mean weight, YMRS and HAM-D scores, leptin levels, and BMI before and after treatment in the patients were presented in table 1.

The change in leptin levels correlated with the change in BMI ($r = 0.58$, $p < 0.05$) and that in the weight ($r = 0.57$, $p < 0.05$). There was a significant positive correlation between the changes in leptin levels and the duration of illness ($r = 0.67$, $p < 0.05$). The change in total YMRS scores correlated with change in leptin levels ($r = 0.81$, $p < 0.01$) and that in the weight ($r = 0.76$, $p < 0.01$).

Discussion

The results presented here provides preliminary evidence that 8-week administration of Li in patients with bipolar disorder affects the body weight, and serum leptin levels. Moreover, we demonstrate that increases in weight and BMI, and clinical efficacy, as indicated decrease in total YMRS scores, are associated with leptin levels.

The mechanism of Li-induced weight gain is incompletely understood. It has been proposed several mechanisms of Li-associate weight gain, i.e. Li-induced lowering in metabolic rate, increased food intake secondary to improvement on mood, etc. [16]. It has been described that interaction between Li and serotonin receptors may be associated with Li-induced weight gain [17]. An interaction between leptinergic and serotonergic systems has been demonstrated in the central nervous system [18]. Serotonin being an important satiety factor is well-known. Despite of the fact that it has not been well-understood which serotonin receptors are critical, increase in serotonin at different serotonin receptors has been demonstrated to decrease food intake [19]. Fluoxetine, a selective serotonin reuptake inhibitor, has been reported to reduce the plasma leptin levels in rats [20] and it has been noted that leptin administration stimulated serotonin turnover [21]. Chronic administration of Li has increased the serotonin release in the lateral hypothalamus [17]. In a study performed by Hastings et al. [22] to investigate the interactions between leptinergic and neurotransmitter systems of the rat brain, it has been reported that leptin had no significant effect on hypothalamic noradrenaline overflow, while leptin perfusion induced a significant increase in 5-hydroxyindoleacetic acid (5-HIAA) overflow from the hypothalamus. In the pathogenesis of Li-induced weight gain, the exact role of leptin and serotonin which seem to be related with each other has been obscured due to the lack of investigations.

It is worth noting that the present study is limited by a small sample size with a total of 15 patients and by the absence of an available control group. In summary, our results suggest that leptin may be associated with lithium induced weight gain though our sample is too small to allow us to obtain a clear conclusion. Our results need to be confirmed by more comprehensive and detailed further studies with a control group to decipher the exact roles of leptin in weight gain related lithium use.

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