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Assessment of Serum Leptin and Thyroid Hormone Levels among Depressed Women

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Abstract

Objective: There is a substantial amount of evidence suggesting that alteration in some hormones is associated with depression. The aim of the study was to assess the serum level of thyroid hormones and leptin in patients with depression.
Subjects and Methods: In this case-control study, 63 patients with different degrees of depression and 69 healthy, age and sex matched control subjects were selected. The Beck Depression Inventory was used to classify the degree of depression into mild, moderate, and severe. The level of Leptin, thyrotropin (TSH), thyroxine (T4), triiodothyronine (T3) were estimated using commercially available kits and Free T4 index was calculated.
Results: Leptin and T3 levels were significantly decreased and T4 rose in the depressed women as compared to the healthy controls ($P < 0.05$, $P < 0.001$, and $P < 0.001$ respectively). Furthermore, the serum level of leptin was significantly lower and T4 was significantly higher in sever depressed women compared to moderately or mildly depressed women ($P < 0.001$ and $P < 0.01$, respectively).

Conclusion: This study showed that thyroid and leptin hormones malfunction in depressed women. Thus, inclusion of thyroid and leptin screening test in the case of deessed patients might be required in proper management schedules.

Keywords: Leptin; Thyroid Hormones; Depression; Women

Introduction

The World Health Organization (WHO) estimates that during the early the 21st century depression is considered as the second most common debilitating illness worldwide.(1) There is high risk of major depressive disorder for Women of child bearing age. (MDD). The lifetime risk for MDD in the community samples has varied from 10 % - 25 % for women, with peak prevalence between 25 - 44 years of age.(2) During 21st century, successive generations have experienced MDD earlier during their life time, therefore, it seems that more women will become ill during their childbearing ages.(3)

Currently depression is usually treated by antidepressants, having their therapeutic effects through promoting monoaminergic neurotransmission.(3) However, a substantial proportion of depressed patients show no response to the current available antidepressants, and only less than half of the drug-responsive patients experience full remission.(4) Recent studies suggest that leptin, secreted by adipocytes, may be a novel antidepressant.(5, 6) Leptin circulated neurohormones which are produced by adipose tissue in the form of the product of the obese (ob) gene. Which binds to specific receptors in the brain, having the physiological role of decreasing food intake and enhancing energy expenditure.(7) As a result, it has been hypothesized that leptin is associated with the vegetative symptoms of depression, particularly weight alteration and appetite.(6) Leptin itself has shown antidepressant effects in animal models of depression.(8) In addition, it is believed that depression might be characterized by a "low-thyroid function syndrome".(9, 10) During the last few years, a huge number of scientific articles have been published on the subject of the relationships between psychiatric disease and thyroid hormones. These studies have demonstrated the presence of numerous changes in the hypothalamo-pituitary-thyroid (HPT) axis, mainly in patients with depression, but also in patients with other psychiatric diseases.(11) However, reports of endocrine changes in depression are incon-

sistent. Several authors do not find changes in the HPT axis.(12, 13) To our knowledge, the relationship between the changes of serum leptin and thyroid hormones in depressed women has never been determined in Iran. Therefore, we conducted the present study to investigate the relationship between these endocrine hormones and depression in women.

Materials and Methods

Study Population

During 2005 and 2006, in a case-control study a total of sixty – three patients recruited from the outpatient clinic, aging between 14 to 49 years (mean = 33.5 ± 10.2), refered to Shahid Motahari clinic in shiraz, and were diagnosed as having depressive disorder by using Beck Depression Inventory (BDI) after being confirmed by a psychologist and a self administered questionnaire consisting of 21 sets of items.(14) Subjects were included, of whom participants were healthy or had euthyroid. After assessment of the depression level, the study group was categorized into three subgroups: patients with mild depression n = 7, patients with moderate depression n = 15, and patients with severe depression n = 41. The cut-off score for severe versus non severe depression was 23 on the BDI. Sixty-nine healthy women matched for age (mean = 32.1 ± 9) were selected as the control group.

The exclusion criteria included any clinical evidence of cardiovascular or atherosclerotic disease, chronic viral infections, history of cancer, menopause, diabetes, renal or liver diseases, taking vitamin or mineral supplements and antidepressants. Demographic data, any concurrent illness history, and lifestyle habits were collected by the interviews. The study protocol was reviewed and approved by the Ethics Committee of Research Council of the vice-chancellery of Research Affairs of Shiraz University of Medical Sciences.

Measurements: Anthropometric indices were determined for each participant. Anthropometric assessments included measurement of weight and height. Body weight was measured to the nearest 0.1kg using the scale (Seca 713) while the subjects were minimally clothed. Height was determined using measuring tape without shoes, and subsequently body mass index was calculated by dividing weight (kg) by squared height (m^2).

The Participants were given oral and written explanations of the study, including its benefits and procedure. In the beginning of the study, the partici-

pants were asked to read and sign an informed consent form.

Obesity was defined as BM > 29.9 kg/m^2. To calculate waist-to-hip ratio (WHR), the waist circumference was measured in a horizontal plan at the level of the high point of the iliac crest to the nearest 0.1cm. Hip circumference was measured in a horizontal plan at maximum extension of the buttocks. Abdominal obesity was defined as WHR > 0.8.(15) Venous blood samples were collected following an overnight fasting. The Subjects' serum was stored in -70°C until analysis.

Serum leptin, TSH, T4, and T3 were determined by raidioimmunoassay (16), using commercially available kits (Kavoshyar for TSH, T3, T4, and DRG for leptin). The inter-assay coefficient of variation for leptin ranged from 4.1 % to 7.4 % and the intra-assay coefficient of variation was 5 %. The intra-assay coefficient of variations for TSH, T4 and T3 were 3.2 %, 4.5 % and 5.8 % and the inter-assay coefficient variations were 4.2 %, 5.2 % and 6.2 % respectively. Free T_4 Index (FTI) was calculated as $\frac{T_4 \times T_3 RU}{100}$.

Statistical Analysis: Data processing and statistical analysis were performed using SPSS version 11.5 for Windows (SPSS Inc., Chicago, 2006). Continuous variables are presented as mean ± standard deviation (SD), while categorical variables are presented as absolute and relative frequencies. Goodness of fit to normal distribution was investigated by p-p plots and the Kolmogrov-Semirnov test. Differences in the mean values between the groups were evaluated by a one-way analysis of variance (ANOVA) and independent sample t-test. We used bivariate data analysis to check the association between variables. This association was evaluated by Pearson correlation coefficients. Two-tailed P-values were used and statistical significance was considered at P-value < 0.05.

Results

Comparison of characteristics of the patients and controls is presented in Table 1. The result of this comparison shows that there are no differences on age, BMI, waist to hip ratio, percent of body and abdominal obesity between the two groups. The Beck depression inventory indicated that most patients had a severe depression. Forty/one patients (65%) had severe and fifteen (24%) had moderate depression. Also, seven patients (11%) had a mild depression.

As Table 2 shows, the serum concentration of leptin was low, but signifi-

cantly, lower in depressed patients when compared with controls ($P < 0.05$). On the other hand, depressed women had higher serum T_4 levels and lower serum T_3 levels compared to the controls ($P < 0.001$). No significant difference was observed between the two groups in serum TSH levels and Free T_4 Index (FTI). Bivariate analysis indicated that concentration of leptin was correlated with all indices of adiposity: $r = 0.64$ for BMI, $r = 0.61$ for weight, $r = 0.71$ for waist circumference and $r = 0.59$ for WHR (all $P < 0.001$).

Endocrine parameters in the serum of patients with varying degrees of depression are given in Table 3. As shown, serum leptin levels were significantly lower in patients with severe depression when compared with mild and moderate depression ($P < 0.001$). In addition, patients with more severe depression had a higher mean T_4 compared with mildly and moderately depressed patients ($P < 0.01$).

Discussion

In this study, we revealed the differences on the levels of leptin and thyroid hormones between patients with depression and healthy subjects. We particularly investigated the relationship between serum levels of these hormones with severity of depression. To the best of our knowledge, this study is the first to investigate these hormones in women with different degrees of depression.

The present study demonstrates that serum levels of endogenous leptin, a hormone produced by white adipose tissue, were decreased in depressed women. There are conflicting data in the literature regarding the relationship between depression and leptin. Decrease in leptin concentration of our patients has been shown in a number of other studies. (17, 18) (Low cerebrospinal fluid levels of leptin have been found in depressed females, but not in males, who had made a suicide attempt).(19) However, some studies have reported an elevated leptin level among depressed patients.(20, 21) Furthermore, Deuschle et al have found either no association or higher leptin levels in depressed individuals.(22) Some of these discrepancies may reflect a diverse range of confounders arising from different subject selection criteria and recruitment strategies. The mechanisms underlying leptin deregulation pertaining to depression remain unclear and the question of whether depression or deregulation of leptin levels is the primary event remains still unanswered. In an animal study, Plot-

sky ,et al (23), showed that rats subjected to two weeks of chronic unpredictable stress displayed a rapid fall in plasma leptin levels in response to acute restraint stress. They reported that (this response of leptin is opposing to sensitized surge of corticosterone in the same animals, which has been considered as a pathophysiological feature of hyperactive hpothalamic-pituitary-adrenal axis (HPA) in human depression. The HPA axis abnormality is characterized by the overproduction of corticotrophin-releasing hormone (CRH), elevated cortisol levels, exaggerated cortisol response to adrenocorticotropic hormone (ACTH) and enlargement of the pituitary and adrenal glands).(24) Some evidence reveals that leptin modulates HPA function. Valuable information have been provided on the relationship between leptin and HPA axis in the studies on mouse models with mutations in the leptin gene (ob/ob) or the leptin receptor gene (db/db). Hypercorticosteronemia was observed in both ob/ob and db/db mice.(25, 26) Furthermore, leptin decreases mRNA expression of CRH in the paraventricular nucleus hypothalamus (PVN) (27) and CRH release from the hypothalamus.(28) These findings suggest that the inhibitory effect of leptin on ACTH and corticosterone is probably mediated by hypothalamus CRH. Moreover, studies have suggested that leptin can enhance the negative feedback effect of glucocorticoids on CRH.(29) Taken together, these clinical observations suggest a link between reduced leptin levels and major depression. One possible explanation for the seemingly contradictory data may be that leptin levels are influenced by certain factors such as age, sex, sample size, body mass status, and comorbidity with other disorders. Another interpretation is that leptin insufficiency may only occur in a subpopulation of depressed patients. (While leptin's antidepressant efficacy in humans awaits clinical investigations, it is speculated that depressed patients with low leptin levels might have a better chance to respond to leptin treatment).(9)

In this study, we have also found that depressed women have increased serum T_4 compared to healthy controls. Serum T_4 levels, both total and non-protein-bound (free), are consistently found ranging from normal to increased in groups of depressed patients.(9, 10) The different findings might be explained by different severities of depression among the patients studied, since some studies have found a correlation between the severity of

depression and serum T_4 levels.(9) We have also found a positive correlation between the severity of depression and serum T_4 levels. An additional explanation might be that a depressed patient is often in a state of semi-starvation, and thus may present changes in the HPT-axis similar to those seen in patients with nonthyroidal somatic illness, elevated serum T_4 and reduced serum T_3. Turnover studies using radio-labeled T_4 in a small group of depressed patients have demonstrated that also the daily production rate of T_4 is significantly increased, by 30 % .(9) Increased production rate of T_4 in depressed patients thus suggests that the thyroid gland might be stimulated abnormally in the depressed patients. In contrast, serum T_3 levels in depressed patients are often found normal, but severely studies have found reduced levels, typically in more severely depressed patients.(9, 10) We have also found that depressed women have decreased serum T_3 compared to healthy controls. Serum T_3 levels are influenced by numerous factors which may all be present in the depressed patient: starvation, concomitant somatic illness and changes (increase) in cortisol levels.(9) When present, these factors all tend to decrease the serum T_3 levels.(9) However, since cortisol levels were not measured in our subjects, it is unknown as to whether serum cortisol concentrations were compromised in the depressed group. Kirkegaard et al have found unaltered free T_3 levels in depression.(10) The daily production rate of T_3 in un medicated, moderately depressed patients has been studied using tracer turnover techniques, and T_3 production rate was found normal.(9) The combination of an increased T_4 and decreased T_3 levels in depression suggests a reduced deiodination of T_4 into T_3, as also seen in nonthyroidal illness. The reduced conversion of T_4 into T_3 might be due to reduced deiodination enzyme activity. However, in which compartment of the human body this takes place is at present unknown. This could in theory be the brain, but unfortunately we are not aware of any data on intracerebral T_3 content or cerebrospinal fluid levels of T_3 in depression.

Furthermore, we found no significant difference between the groups for serum TSH levels. Some studies have reported lower levels of serum TSH among depressed individuals (9), while others have found either no association or higher serum TSH levels in depressed individuals.(9, 10) However, a great part of these discrepancies may be a result of the variability in the

methods used, the population analyzed, study outcomes or types of study design.

Our study may have some limitations in data gathering as in all cross-sectional studies. First, as with all observational studies, our results could be biased by unrecognized confounders. Second, the cross-sectional study does not allow us to conclude causal relationships. Third, we couldn't assess nutrient intakes (including vitamins and minerals) of the participants.

In conclusion, our data indicate a deregulation of circulating levels of leptin and thyroid hormones in depression. Thus, identification of the underlying molecular mechanisms in depression, that seems to include numerous changes in the thyroid hormones and leptin, may serve as an important guide for developing potentially new treatment modalities in this group of patients at risk for other psychiatric diseases.

Table 1. Demographic and Anthropometric Characteristics of Patients and Controls

Variables	**Patients (n = 63)**	**Controls[a] (n = 69)**	**Between groups P - value**
Age (years)	33.5 ± 10.2	32.1 ± 9.0	0.37
Weight (Kg)	65.6 ± 11.1	71.3 ± 15.7	0.12
Height (Cm)	159.5 ± 5.9	159.5 ± 5.6	0.88
Body mass index (Kg/m^2)	25.7 ± 4.1	27.0 ± 5.5	0.11
Waist circumference (Cm)	82.2 ± 10.6	84.1 ± 12.4	0.24
Hip circumference (Cm)	102.1 ± 7.0	104 ± 9.3	0.34
Waist-to-hip ratio	0.8 ± 0.07	0.8 ± 0.10	0.87
Abdominal obesity (%)	51.5	38.5	0.19
Depression status			
Mild (n, %)	7 (11%)	N.A	
Moderate (n, %)	15 (24%)	N.A	
Severe (n, %)	41 (65%)	N.A	

[a] All values are means ± SD, N.A: not applicable

Table 2. Endocrine Parameters of Patients and Controls

Parameters	Patients (n = 63)	Controls [a] (n = 69)	P - value
Leptin (ng/mL)	16.82 ± 7.28	19.58 ± 8.80	0.04
T_4 (nmol/l)	137.4 ± 25.6	121.3 ± 16.8	< 0.001
T_3 (nmol/l)	5.86 ± 1.26	7.78 ± 0.84	< 0.001
TSH (mU/l)	1.96 ± 1.13	2.04 ± 1.19	0.67
Free T_4 index (pmol/l)	2.48 ± 0.57	2.43 ± 0.52	0.64

[a] All values are means ± SD, T_4: thyroxine, T_3: tri-iodothyronine, TSH: thyrotropin

Table 3. Endocrine Parameters of the Patients with Different Degrees of Depression

Parameters	Mild (stage I) (n = 7)	Moderate (stage II) (n = 15)	Severe (stage III) (n=41)	P- value[a]
Leptin (ng/mL)	22.38 ± 8.05[b, c]	20.56 ± 4.89	14.76 ± 7.13	0.004
T_4 (nmol/l)	132.78 ± 14.32[d]	138.45 ± 17.36	141.35 ± 32.20	0.04
T_3 (nmol/l)	6.34 ± 1.82	6.21 ± 1.84	5.48 ± 2.16	0.78
TSH (mU/l)	2.27 ± 1.12	2.37 ± 1.13	1.78 ± 1.11	0.18
Free T_4 index (pmol/l)	2.00 ± 0.43	2.40 ± 0.51	2.56 ± 0.57	0.06

[a] P-Value derived from one-way ANOVA that used to evaluate differences in the endocrine parameters between groups.

[b, d] Significantly different from patients with severe depression: [b] $P < 0.01$, [d] $P < 0.05$.

[c] significantly different from patients with moderate depression ($P < 0.01$).

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