

# Assessment of Serum Tri-Iodothyronine (T3), Thyroxin (T4) and Thyroid-Stimulating Hormone (TSH) Levels Among Patients With Major Depressive Disorder (MDD) in Hamedan, Northwestern Iran

Seyed Mehrdad Kassaei,<sup>1\*</sup> Rahim Ahmadi,<sup>1</sup> Asghar Seif,<sup>2</sup> and Sedigheh Molaei<sup>3</sup>

<sup>1</sup>Department of Physiology, Faculty of Basic Sciences, Hamedan Branch, Islamic Azad University, Hamedan, IR Iran

<sup>2</sup>Department of Statistics, Faculty of Basic Sciences, Bu-Ali Sina University, Hamedan, IR Iran

<sup>3</sup>School of Medicine, Student Research Committee, Qom University of Medical Sciences, Qom, IR Iran

\*Corresponding author: Seyed Mehrdad Kassaei, Department of Physiology, Faculty of Basic Sciences, Hamedan Branch, Islamic Azad University, Hamedan, IR Iran. Tel: +98-8114494001, Fax: +98-8114494010, E-mail: igits071@gmail.com

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## Abstract

**Background:** Depression is one of the most common psychiatric disorders. Over the last few years, the relationship between the hypothalamic-pituitary-thyroid (HPT) axis and depression has been the focus of increasing attention.

**Objectives:** In this study, the serum levels of T3, T4, and TSH in patients with major depressive disorder have been compared to the healthy adults in Hamedan, northwestern Iran.

**Patients and Methods:** In this case-control study, serum levels of T3, T4, and TSH were measured in 32 patients with major depression, diagnosed according to the Beck Depression Inventory (BDI), who were referred to the Hamedan psychiatric hospital and were age- and sex-matched normal adults. Sampling was conducted through convenience sampling in a completely randomized design. Data were analyzed using an independent t-test and a one-way analysis of variance (ANOVA) test. A logistic regression model was used for depression occurrence probability prediction.

**Results:** Serum T4 and TSH levels were significantly higher in depressive patients than in the control group ( $P = 0.01$ ), whereas there was no significant difference in T3 serum levels between the two groups ( $P = 0.08$ ). The serum TSH level was significantly higher in depressive patients compared to non-depressive patients ( $P = 0.001$ ). According to logistic regression analysis, a one unit increase in serum T4 or TSH levels may enhance non-clinical depression probability by 1.3 or 1.7 times and clinical depression probability by 1.2 or 2.9 times, respectively.

**Conclusions:** Serum T4 and TSH levels in depressive patients were found to be significantly higher than those of the control group, indicating the association between serum T4 and TSH levels and depression in the subjects in 2010 - 2011 in Hamedan, northwestern Iran.

**Keywords:** Major Depressive Disorder, Tri-iodothyronine, Thyroxine, Thyroid Stimulating Hormone, Logistic Models

## 1. Background

Over the last few years, many researchers have focused on the connection between thyroid function and psychiatric disorders. Psychiatric syndromes associated with endocrine dysfunction include mood disturbances, anxiety, cognitive dysfunction, dementia, delirium, and psychosis. An estimated 22% - 26% of women and 8% - 12% of men have experienced some form of depression during their lifetimes (1). Depression is the most prevalent mental disorder, and it is thought to be the most common cause of human disability. Studies that followed the global burden of disease (GBD) approach of the World Health Organization (WHO) in 1997 found that unipolar depression was ranked fifth among other diseases and was projected to rise to the second rank by the year 2020 (2). Many studies have implicated thyroid hormone effects on mood and

cognitive functioning. Five to 10% of people with depression suffer from thyroid dysfunction (3). Studies show that hypothyroidism is accompanied by depression and that hyperthyroidism is accompanied by sleeplessness and agitation (4). Some studies reported elevated levels of total thyroxine (T4) and free thyroxine (FT4) in acute depression while other studies do not support these findings (5, 6).

Despite many efforts to standardize the classification of depressive disorders, they remain complex and ill-defined diseases, possibly because their diverse subtypes have different pathogeneses and biochemical abnormalities. Over time the classification has changed making it difficult to interpret previously published data (7). On the other hand, thyroid function testing is more frequent than other endocrine screening to evaluate mood disorders. There is evidence indicating that hypothyroidism

may produce symptoms and signs that present clinically as depression, dysthymia, or lethargy, but it is not all-or-none phenomenon (8). Also, there are conflicting data in the context of thyroid function alterations during depression. Additionally, thyroid hormone parameters are influenced by climatic, genetic, and regional factors (9).

## 2. Objectives

Regarding the mutual association between thyroid gland function and mood changes and the conflicting data in this area, we determined to conduct this case-control study to assess serum T3, T4, and TSH levels among patients with a major depressive disorder (MDD) in Hamedan, northwestern Iran.

## 3. Patients and Methods

### 3.1. Patients

In this case-control study, the participants were 32 patients who were referred to the psychiatry hospital in Hamedan from 2010 to April 2011. After the diagnosis of major depressive disorder in the participants, we selected them as our subjects based on the following criteria: 15 - 50 years of age, first incidence of major depression in their lifetime, no prior antidepressant intake, and lack of any previous thyroid, kidney, liver, heart or rheumatic disorders or diseases. Also, pregnant women were excluded from the study on the basis of the human chorionic gonadotropin (HCG) assay.

Thirty-two normal, age- and sex-matched adult volunteers chosen through convenience sampling with a completely randomized design were accepted to take part in the study. The BDI test for major depression was used to measure depression severity independent of a patient's national culture. The BDI is a questionnaire completed by the participants and includes 21 items: mood, pessimism, past failure, loss of pleasure, guilty feelings, punishment feelings, self-dislike, self-criticalness, suicidal thoughts or wishes, crying, agitation, loss of interest, indecisiveness, worthlessness, loss of energy, changes in sleeping pattern, irritability, changes in appetite, concentration difficulty, loss of interest in sex, and tiredness or fatigue. Each item is scored from zero to three. Literate people over the age of 13 years are able to respond to this questionnaire. The reliability of 78%, validity of 73%, and internal consistency of 86% of this questionnaire have been proven in Iran (10, 11). Therefore, the BDI test was used to determine the degree of depression.

Also, socio-demographic data were collected using a questionnaire which included questions on age, sex, marital status, religion, occupation, education, body mass

index (BMI), dietary habits, socio-economic status, drug abuse, and parental death before the age of (12)

Consent forms were signed by participants, parents, or guardians after they understood the procedures involved in the study. Participants were made aware that any nominal or individual information about their test results would remain confidential due to legal considerations concerning the BDI test (12, 13).

### 3.2. Questionnaire Data Interpretation

The distribution frequency of depression based on the BDI test (1961) indicates the variable of depression level which was defined as having four sublevels, including 0 - 15, 16 - 30, 31 - 46, and > 47. Scores correspond to non-depressive or control, minor, moderate, and severe depression, respectively (14). Each subject could only be assigned to one of the above-mentioned levels. In another case, as a new clinical layout, a BDI score lower than 21 indicates clinically non-depressive, and a score of 21 or more indicates clinically depressive patients (15).

### 3.3. Thyroid Hormone Assay

Fasting plasma levels of T3, T4, and TSH were measured to indicate the hypophysis and thyroid glands' functions prior to treatment. After separation of serum, T3 and T4 were measured using an enzyme-linked immunosorbent assay (ELISA) and TSH was measured using a sandwich ELISA protocol employing monoclonal antibodies using commercially available kits [IMMUNOTECH A, BECHMAN COULTER/REF 2121].

### 3.4. Statistical Analysis

Data from convenience samplings in a completely randomized design were analyzed using SPSS software. Chi-square ( $\chi^2$ ) was used to indicate the relationship between the nominal variables. An independent t-test was conducted to compare the serum levels of T3, T4, and TSH following confirmed data normality through the Kolmogorov-Smirnov (KS) test. A student t-test and a one-way ANOVA with multiple comparison testing were applied to compare quantitative variables; i.e., the effect of depression level on T3, T4, and TSH. The Bonferroni post hoc test was conducted to compare responses over the levels of the tested factors.

## 4. Results

There was no significant difference between the depressed and normal groups with respect to age, sex, marital status, religion, occupation, education, body mass index, dietary habits, socio-economic status, drug abuse, and

parental death before age 13. Based on the BDI, 13 (20.31%), 10 (15.62%), and 9 (14.07%) participants in the depressed group suffered from minor, moderate, and severe depression, respectively. Also, 37 (57.8%) and 27 (42.2%) participants were non-clinically depressive and clinically depressive, respectively. T4 and TSH serum levels of depressive patients were significantly higher than those of healthy people ( $P = 0.01$ ); however, the T3 serum level was not significantly different between the two mentioned groups ( $P = 0.08$ ). Of all such comparisons between clinical and non-clinical depressive patients, only the TSH serum levels were significantly different ( $P = 0.001$ ) (Table 1).

**Table 1.** Serum T3, T4, and TSH Levels in Clinically and Non-Clinically Depressive Patients<sup>a, b</sup>

Groups	Non-Clinically Depressive (n = 37)	Clinically Depressive (n = 27)	P Value
T3, ng/mL	1.21 ± 0.47	1.23 ± 0.56	0.88
T4, µg/dL	7.60 ± 2.91	8.95 ± 2.39	0.053
TSH, mIU/L	1.98 ± 1.15	3.12 ± 1.57	0.001*

<sup>a</sup>Serum T3, T4, and TSH levels are presented as mean ± SD.

<sup>b</sup>P values indicate comparison of the two mentioned groups. Clinical depression is revealed by a score of 21 or more on the BDI test; non-clinical depression is revealed by a score lower than 21 on the BDI test.

The effect of the depression level variable on T3, T4, and TSH serum levels was measured by the eta-squared index ( $\eta^2$ ). The eta-squared value indicates the impact of an independent variable on the dependent variable with a range of zero to one. A  $\eta^2$  above 0.14 implies a major effect (16). The results are briefly reported as follows: the effect of the depression level variable on T3 was significant [ $F(3,60) = 6.4, P = 0.0005, \eta^2 = 0.27$ ]; its effect on T4 was also significant [ $F(3,60) = 7.2, P = 0.0005, \eta^2 = 0.26$ ]; and its effect on TSH was significant also [ $F(3,60) = 9.6, P = 0.005, \eta^2 = 0.32$ ]. Comparison of the non-depressed group with the three levels of mild, moderate, and severely depressive patients indicates that the minor depressive T3 serum levels were significantly higher than those of the non-depressive patients ( $P = 0.02$ ), while the difference was not significant concerning moderate or severely depressive patients. Serum levels of T4 of minor ( $P = 0.02$ ) and moderate ( $P = 0.005$ ) depressive patients were significantly higher than those of the non-depressive patients, although no significant difference was observed between the severely depressive and control groups. Also, the TSH serum level was significantly enhanced in severely depressive patients compared with patients in the non-depressive group ( $P = 0.0005$ ) (Table 2).

All subjects were included in the model, and its significance was verified by an Omnibus test ( $\chi^2 = 14.2, df = 2, P = 0.001 < \alpha = 0.01$ ). Logistic regression was conducted to pre-

dict a participant's risk of depression using T3, T4, and TSH as independent variables. Since the model indicated that only TSH and T4 reliably predict depression occurrence probability in every individual, logistic regression was performed excluding T3, resulting again in the significance verification of the model. It was also revealed that a one unit increase in the serum T4 or TSH levels may enhance non-clinical depression probability by 1.3 or 1.7 times, respectively (the coefficients 0.31 and 0.55 in the following model are the natural logarithm of the odds). The model is:

$$\text{Logit} = -3.9 + 0.31 T4 + 0.55 TSH$$

Moreover, by conducting logistic regression to predict the probability of clinical depression using independent variables T3, T4, and TSH (excluding T3), the following result was obtained:

$$\text{Logit} = -4.58 + 0.28 T4 + 0.73 TSH$$

In this case, a one unit increase in the serum T4 or TSH levels may increase clinical depression probability by 1.2 or 2.9 times, respectively. The important point is that these models may predict whether the patient will be depressed or not in the future, if T4 and TSH serum levels are measured.

## 5. Discussion

The relationship between the HPT axis and depression has long been recognized. Since the current study has been geared toward patients with no previous histories of psychiatric medications or depression attacks, it is a critical investigation which reveals the relationship between the mentioned axis and depression more clearly. In this study, the disease onset age was 32 years. A significant increase in the serum T4 and TSH levels in the depressed group compared to the control is consistent with the studies conducted by Das and Gold (17, 18) which point to the presence of thyroid dysfunction among the depressives which is most often characterized as a Lower Thyroid Syndrome. Although these results appear to contradict previous studies, which have reported serum T3, T4, and TSH levels in depressive patients to be in the normal range (19), and also studies by Fava which mentioned hypothyroidism and hyperthyroidism as extremely uncommon disorders in depressed patients (20), there is also research which indicates that depressive patients suffer from subclinical hypothyroidism (SCH) (21). Several studies have suggested that the high level of thyroxine in depression is due to an enhanced TSH level (22, 23). There are studies that reported the relationship between depression severity and the serum levels of T4 (24). According to the logistical relationship between T4 and TSH serum levels and depression, the lower levels of T4

**Table 2.** Serum T3, T4, and TSH Levels in Non-Depressive or Control Patients and Patients With Different Depression Levels<sup>a,b</sup>

Groups	Non-Depressive (n = 33)	Depressive		
		Mild (n = 13)	Moderate (n = 10)	Severe (n = 9)
T3, ng/mL	1.11 ± 0.36	1.55* ± 0.57	1.53 ± 0.54	0.80 ± 0.36
T4, µg/dL	7.30 ± 2.90	9.70* ± 1.96	10.41** ± 1.75	6.48 ± 0.94
TSH, mIU/L	2.04 ± 1.11	2.10 ± 1.33	2.48 ± 1.33	4.66** ± 1.41

<sup>a</sup>Serum T3, T4, and TSH levels are presented as mean ± SD.

<sup>b</sup>\* and \*\* indicate P < 0.05 and P < 0.01, respectively. 0 - 15, 16 - 30, 31 - 46, and > 47 BDI scores represent non-depressive control, minor, moderate, and severe depression, respectively.

can reduce the likelihood of depression occurrence. Sub-clinical hypothyroidism may reduce the depression occurrence probability (25). Studies in Italy and the United States suggest the importance of psychiatric evaluation in patients affected by subclinical hypothyroidism and emphasize that thyroid hormone augmentation is effective for nonresponders to antidepressant agents, including serotonin specific reuptake inhibitors (26, 27), although it has not been studied extensively. In our study, there was no significant change in the serum T3 levels in depressed patients when compared to those in the control subjects. In contrast to this finding, there are studies that have shown reduced serum levels of T3 in severe depression (28). On the other hand, our findings indicated that the serum TSH level was higher in clinically depressive patients than non-clinically depressive patients which showed the role of the HPT axis in clinical depression occurrence. Our findings, for the first time, demonstrated an association between serum T4 and TSH levels and the severity of depression in a logistic form in which a one unit increase in serum T4 or TSH levels may enhance the non-clinical depression probability by 1.3 or 1.7 times and the clinical depression probability by 1.2 or 2.9 times, respectively. However, further research is required to obtain more substantial data in this area.

### 5.1. Conclusion

The serum T4 and TSH levels of depressive patients were significantly higher than those of the control group, indicating an association between serum T4 and TSH levels and depression occurrence in Hamedan, northwestern Iran (2010 - 2011). However, serum levels of T3 were not significantly different between the two groups. Also, the effect of the depression level variable on T3, T4, and TSH serum levels was confirmed. These data suggest the role of the hypothalamic-pituitary-thyroid axis in depression. Therefore, T4 and TSH levels must be considered in the hormonal treatment of depression.

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