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Evaluation of Anxiety and Depression among a Sample of Hypothyroidism-Treated Iraqi Patients

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Abstract

Hypothyroidism is the most prevalent thyroid disorders worldwide Hypothyroidism manifestations are wide spectrum, affecting various systems in human body including the nervous system, which can cause neuropsychiatric symptoms such as anxiety, depression and diminishing in attention, memory and executive function, to investigate the level of anxiety and depression in patients with hypothyroidism receiving levothyroxine treatment. A cross-sectional study was conducted at Baghdad Center for Nuclear Medicine and Radiation Therapy from March to June 2022. The study population included patients of both genders, aged 18-65 years, diagnosed with hypothyroidism, were receiving levothyroxine treatment and have achieved euthyroid state for at least 2 months prior to their enrolment in the study. Based on levothyroxine dose, the enrolled patients were divided into two groups: low dose group < 1.7 µg/kg/day and high dose group ≥ 1.7 µg/kg. Hospital Anxiety and Depression Scale (HADS) was used for the evaluation of anxiety and depression. The mean age of the participants was 40.35 ± 9.5 years with mean body mass index of 30.61 ± 5.72 kg/m2. The mean scores of anxiety and depression for the total sample are 8.72 ±3.46 and 7.80 ±2.83; respectively, there was statistically non-significant difference for anxiety and depression scores between the low dose group and the high dose group. The anxiety and depression symptoms were still in place even when the patients were in euthyroid state. However, clinical characteristics did not significantly influence the scores of those mental conditions. Hypothyroid patients need to be monitored for anxiety and depression in addition to the routine monitoring of thyroid function.

Keywords: Hypothyroidism, Levothyroxine, Anxiety, Depression.

تقييم القلق و الكأبة عند عينة من المرضى العراقيين الذين يتعالجون من قصور الغدة الدرقية

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الخلاصة

قصور الغدة الدرقية يعتبر من اكثر امراض الغدة الرقية شيوعا حوال العالم. تكون اعراض مرض قصور الغدة الدرقية متعددة وتأثيرها على مختلف اعضاء جسم الانسان ومن ضمنها الجهاز العصبي. و من الممكن ان يسبب اعراض عصبية ونفسية مثل القلق الكأبة و قلة في الانتباه و الذاكرة والوظائف التنفيذية. الهدف من الدراسة هو التحقق من وجود القلق والكأبة في مرضى قصور الغدة الدرقية الذين يتلقون علاج الليفوثايروكسين. الوسائل لتحقيق الهدف تتضمن دراسة مقطعية لمرضى قصور الغدة الدرقية و نفدت الدراسة في مركز بغداد للطب النووي والعلاج الاشعاعي من اذار الى حزيران ٢٠٢٢. واشتملت عينة المرضى المشاركين تكون اعمارهم من ١٨الى ٦٥ سنة من كلا الجنسين , مشخصين بمرض قصور الغدة الدرقية وقد وحققوا مستويات طبيعية من هرمونات الغدة الدرقية لمدة شهرين على الاقل قبل اشتراكهم في الدراسة. اعتمادا على جرعة الليفوثايروكسين تم تقسيم المرضى الى مجموعتين: مجموعة منخفضة الجرعة (اقل من ١,٧مايكروغرام لكل كغ في اليوم) و مجموعة عالية الجرعة (اكبر او يساوي ١,٧ مايكروغرام لكل كغ في اليوم). و استخدام استبيان مخصص لتقييم القلق والكأبة. النتائج: ان معدل العمر للمشاركين كان ٤٠,٣٥±٩,٥ سنة و معدل مؤشركتلة الجسم هو ٣٠,٦١±٥,٧٢ كغم لكل م[٢] . كان معدل مجموع نقاط القلق والكأبة لكل المشاركين هو ٨,٧٢±٣,٤٦ و ٧,٨٠±٢,٨٣ على التعاقب, واحصائيا كان اختلافا ليس بذي اهمية بين نتائج القلق والكأبة بين المجموعتين . الاستنتاج: وجود اعراض القلق والكأبة في المرضى على الرغم من المستويات لطبيعية للغدة الدرقية. مع ذلك الخصائص السريرية للمشاركين كأن تأثيرها ليس بذي اهمية على مؤشرات هذه الحالات النفسية. يتوجب مراقبة القلق والكأبة لدى مرضى قصور الغدة الدرقية بالاضافة الى المتابعة الروتينية لوظائف الغدة الدرقية.

الكلمات المفتاحية: قصور الغدة الدرقية، الليفوثايروكسين، القلق،الكأبة

Introduction

Hypothyroidism is one of the main endocrine morbidities that is characterized by deteriorating thyroid hormone production. Thyroid hormones, thyroxine (T4) and triiodothyronine (T3), play a crucial role in all aspects of each organ metabolism and function including the brain. Hypothyroidism can be linked with different psychiatric disorders such as depression, anxiety and alterations in mood and cognition[(1)].

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Hypothyroidism is characterized by a range of signs and symptoms that affect different body systems including: mood disturbances; anxiety and depression. These symptoms can be reversed via the standard therapy with levothyroxine; however, some patients may still have persistent symptoms regardless of normalizing thyroid hormones levels [2, 3]. In Iraq, the prevalence of hypothyroidism has been studied in different cities [4- 7] where it was found to be 3.2% and 12.5% in Baghdad and Basrah; respectively [4, 5].

Various studies have explored the prevalence of anxiety and depressive manifestations in hypothyroid patients. One study was conducted in Turkey which indicated that anxiety and depression scores were significantly higher in patients compared to the control group [8]. In addition, a meta-analysis study showed strong indications of higher frequency of depression and anxiety in patients with hypothyroidism [9]. Furthermore, another study was performed in Germany that recognized the untreated hypothyroidism is correlated with depression and anxiety [10]. The standard treatment for overt hypothyroidism is levothyroxine [11]. The impact of levothyroxine therapy on anxiety and depression in patients suffering from hypothyroidism is still an ambiguous and questionable issue. Several investigators have reported that the hypothyroid patients had mood symptoms in spite of the treatment with levothyroxine and the achievement of euthyroidism [12, 13]. On the other hand, a different study had examined the anxiety and depression scores in a group of patients with clinical hypothyroidism before and after levothyroxine treatment and concluded that these scores were reduced after the treatment and were less than the control group [14]. Hence, the efficiency of levothyroxine therapy on alleviating depression and anxiety symptoms remains undetermined.

In Iraq, there were several studies that have investigated anxiety and depression in different population, and found considerable levels of these mental conditions among the studied populations. One study has evaluated depression in patients with cancer and found that these patients had a significant level of depression [15]. Another study has assessed the level of anxiety and depression in health care workers after recovery from coronavirus disease of 2019 (COVID-19). It was shown that only 29.7% and 43.2% of the participants had normal levels of depression and anxiety; respectively [16]. Furthermore, anxiety and depression were evaluated among the students of health care colleges, and it was found that 45.9% and 52.1% of the participants had scores of depression and anxiety symptoms; respectively [17].

To the extent of our knowledge, this is the first study in Iraq that was concerned with anxiety and depression in hypothyroidism-treated patients.

The aim of this study was to investigate the level of anxiety and depression in patients with hypothyroidism receiving levothyroxine treatment.

Methods

Study design

This was a cross-sectional study which was conducted at the outpatient clinic in Baghdad Center for Nuclear Medicine and Radiation Therapy in Baghdad from March to June 2022. The study was approved by the Scientific Committee of the College of Pharmacy/University of Baghdad and Medical City Directorate/Ministry of Health, Verbal consent was obtained from the patients before their enrolment in the study.

Study population

The study population was patients diagnosed with hypothyroidism and receiving levothyroxine treatment who consented to participate in the study. The inclusion criteria included patients of either gender, aged from 18 to 65 years and prior to their enrolment in the study they have received levothyroxine treatment and have achieved euthyroid state for at least 2 months which is the time required to reassess TSH level after initiating levothyroxine dose and after any dosage change [18]. The excluded patients were: pregnant or lactating women, patients who have cardiovascular disease, congenital hypothyroidism, hepatic and renal impairment and those who have serious psychiatric diseases (e.g., schizophrenia) or those taking medications that can disturb mood (e.g., antipsychotics). The participants were enrolled consecutively (according to their attendance to the study center) and allocated into two groups depending on the daily dose of levothyroxine: low dose group < 1.7 µg/kg/day and high dose group ≥ 1.7 µg/kg [19].

Data collection

Socio-demographic and clinical data were obtained directly from the patients during face to face interview. The socio-demographic data included age, gender, body mass index, educational level, marital status, occupational status and smoking habit. The clinical data included levothyroxine dose, duration of the treatment and the disease, concurrent medical conditions and medications, thyroid function tests (TSH, TT4 and TT3 levels).The quantitative measurements for TSH, TT4 and TT3 in this study were performed by TOSOH AIA System Analyzer.

The assessment of anxiety and depression

The assessment of anxiety and depression was fulfilled using the validated Arabic version for Hospital Anxiety and Depression Scale (HADS) questionnaire [20]. The researcher was asking the questionnaire's questions and recording the patients' answers during face to face interview. The HADS consists of 14 items which is divided into two subscales; anxiety (7 items) and depression (7

items), which are rated on a 4-point scale (from 0-3). The ratings in each subscale are computed via summing the corresponding items, with a total of 21 for each subscale. A grade of 0-7 is considered normal, 8-10 as a borderline and 11-21 as case which is defined as confirmed case anxiety or depression [21].

Statistical analysis

Statistical analysis was accomplished via IBM SPSS Statistics for Windows version 25. Continuous variables were presented as mean ± standard deviation (SD) while categorical variables were presented as number and percentages. Independent t- test was used to compare means of anxiety and depression score between both groups. Chi-square test was used for the association between categorical variables. Correlation analysis included Pearson correlation for anxiety and depression scores with normally distributed variables and Spearman correlation for variables that were not normally distributed. P-value of less than 0.05 was considered to be significant.

Results

Total of 60 hypothyroid patients were enrolled in the study and subcategorized into two groups of 30 patients, low-dose group and high-dose group. The socio-demographic features of the patients are presented in Table 1. The mean age of the participants was 40.35 ± 9.5 years with mean body mass index of 30.61 ± 5.72 kg/m^2. The majority of patients were females (85%), married (90%) and unemployed (40%). Regarding the education level, results have shown that 50% of the patients had completed secondary school, and (33.3%) had bachelor degree. About 93% of the patients were nonsmokers.

Table 1. Socio-demographic characteristics of the participants for each group

Variables	Low dose group N (30)	High dose group N (30)	Total N (60)
Age (years) *	43.37 ± 10.19	37.33 ± 7.81	40.35 ± 9.5
BMI (Kg/m^2) *	32.15 ± 5.47	29.07 ± 5.64	30.61 ± 5.72
Gender †			
Male	7(23.3)	2(6.7)	9 (15.0)
Female	23(76.7)	28(93.3)	51 (85.0)
Education level †			
Primary	6 (20)	4 (13.3)	10 (16.7)
Secondary	16 (53.3)	14 (46.7)	30 (50.0)
College	8 (26.7)	12 (40.0)	20 (33.3)
Occupational Status †			
Employed	9 (30)	11 (36.7)	20 (33.3)
Unemployed	21 (70)	19 (63.3)	40 (66.7)
Marital Status †			
Married	28 (93.3)	26 (86.7)	54 (90.0)
Unmarried	2 (6.7)	4 (13.3)	6 (10.0)
Smoking †			
Yes	2 (6.7)	2 (6.7)	4 (6.7)
No	28 (93.3)	28 (93.3)	56 (93.3)

BMI = body mass index,
* Mean ± standard deviation (SD)
† Number (N) (percentage %)

Table 2 shows the clinical characteristics of hypothyroidism for patients in both study groups. The mean levothyroxine doses in the low- and high-dose groups were 81.67 ± 30.74 µg/day and 161.67 ± 35.19 µg/day, respectively. TSH, TT4 and TT3 values were represented as mean ± SD (2.08 ± 1.25 µIU/ml, 8.94 ± 1.61 µg/dl and 1.06 ± 0.17 ng/ml respectively). The median of levothyroxine treatment period was 4 years in low-dose group and 3 years for high- dose group. Regarding the etiology of hypothyroidism, the distribution of the patients showed that the patients who had primary hypothyroidism had the highest percentage in the low-dose group (46.7%), whereas in the high-dose group the highest percentage was 53.3% for patients who had thyroidectomy and radioactive iodine (RAI). The most commonly used medications were vitamin D and metformin tablet. Only five hypothyroid patients suffered from diabetes mellitus.

Hospital Anxiety and Depression scale scores are illustrated in Tables 3 and 4.The mean scores of anxiety and depression for the total sample were 8.72 ±3.46 and 7.80 ±2.83; respectively. Statistically non-significant differences were found when comparing means of anxiety score and depression score between the two study groups. The study results also showed that

the confirmed cases of anxiety were 33.3% of the patients in the low-dose group while in the high dose group the confirmed cases of anxiety were 40% of the patients. Furthermore, the confirmed cases of depression were shown in 20% of patients in the low-dose group compared to 23.3% in the high-dose group. These differences were statistically non-significant (p-value > 0.05).

Table 2. Clinical characteristics of hypothyroidism

Variables	Low dose group N (30)	High dose group N (30)	Total N (60)
Duration of levothyroxine (years) *	4	2	3
Levothyroxine Dose (µg) †	81.67 ± 30.74	161.67 ± 35.19	121.67 ± 51.96
TSH (µIU/ml)	2.5 ±1.05	1.65 ± 1.30	2.08 ± 1.25
TT4 (µg/dl)	8.16 ±1.25	9.720 ± 1.57	8.94 ± 1.61
TT3 (ng/ml)	1.06 ± 0.17	1.06 ± 0.17	1.06 ± 0.17
Etiology of Hypothyroidism ‡			
Primary hypothyroidism **Thyroidectomy** **RAI** **Thyroidectomy & RAI**	14 (46.7) 7 (23.3) 5 (16.7) 4 (13.3)	2 (6.7) 12 (40.0) 0 (0) 16 (53.3)	16 (26.7) 19 (31.7) 5 (8.3) 20 (33.3)
Concomitant medications ‡			
Vitamin D3 tab **Vitamin C tab** **Metformine tab** **Glibenclamide tab** **Glimpride tab** **Oral contraceptive tab**	5 (16.7) 1 (3.3) 2 (6.7) 1 (3.3) 2 (6.7) 0 (0)	5 (16.7) 0 (0) 2 (6.7) 0 (0) 1 (3.3) 1 (3.3)	10 (16.7) 1 (1.7) 4 (6.7) 1 (1.7) 3 (5.0) 1 (1.7)
Comorbid conditions ‡			
Diabetes mellitus	3 (10.0)	2 (6.7)	5 (8.3)

TSH, thyroid stimulating hormone; TT4, total thyroxin; TT3, total triiodothyronine; RAI, radioactive iodine. The reference range of thyroid function test according to the laboratory setting at Baghdad Center for Nuclear Medicine and Radiation Therapy are :TSH = 0.38 – 4.31µIU/ml , TT4 = 4.9 – 11.0 µg/dl, TT3 = 0.79 – 1.58 ng/ml . * Median. † Mean ± SD.‡ Number (N) (percentage %)

Table 3. Hospital anxiety and depression scale score (HADS)

Variables	Low Dose Group N (30)	High Dose Group N (30)	p-value
Anxiety score *	8.70 ±3.27	8.73 ±3.71	0.971
Depression score *	7.70 ±2.33	7.90 ±3.29	0.787

*Mean ± SD

Table 4. Hospital anxiety and depression scale (HADS) scoring sub groups

Variables		Low Dose Group N (30)	High Dose Group N (30)	Total N (60)	P-value*
Anxiety Score †	**Normal (0 – 7)**	11 (36.7)	12 (40.0)	23 (38.3)	0.721
	Borderline (8 – 10)	9 (30.0)	6 (20.0)	15 (25.0)	
	Case (11 - 21)	10 (33.3)	12 (40.0)	22 (36.7)	
Depression Score†	**Normal (0 – 7)**	17 (56.7)	12 (40.0)	29 (48.3)	0.394
	Borderline (8 – 10)	7 (23.3)	11 (36.7)	18 (30.0)	
	Case (11 – 21)	6 (20.0)	7 (23.3)	13 (21.7)	

*Chi-square Test

† Number (N) (percentage %)

The correlation coefficients for anxiety scores with different patients' variables including: levothyroxine dose, TSH, TT4, TT3 and duration of levothyroxine treatment. In addition, the correlations of depression with patients' parameters were measured and were statistically non-significant as shown in Table 5.

Table 5. Correlation of anxiety score and depression score with different patient's variables

Variables	Anxiety score N(60)		Depression score N(60)	
	r	P-value	r	P-value
Levothyroxine Dose (µg)*	-0.015	0.911	0.076	0.564
Duration of levothyroxine (years) ‡	0.138	0.294	0.138	0.294
TSH (µIU/ml)*	0.123	0.350	0.047	0.722
TT4 (µg/dl)*	-0.059	0.653	-0.087	0.507
TT3 (ng/ml)*	0.161	0.220	0.019	0.885

r=correlation coefficient; * Pearson correlation; ‡ Spearman correlation

In addition, the correlation of Hospital Anxiety and Depression Scale (11-21) scores was statistically non-significant with levothyroxine dose, duration of levothyroxine therapy, TSH, total T4 and total T3 levels (Table 6).

Table 6. Correlation of hospital anxiety and depression scale (11-21) scores with various patients' variables

variables	Anxiety score N(22)		Depression score N(13)	
	r	P-value	r	P-value
Levothyroxine Dose (µg)*	0.173	0.442	0.463	0.111
Duration of levothyroxine (years) ‡	0.095	0.675	-0.334	0.264
TSH (µIU/ml)*	-0.186	0.408	-0.259	0.392
TT4 (µg/dl)*	0.090	0.691	0.439	0.133
TT3 (ng/ml)*	-0.280	0.207	0.028	0.928

r= correlation coefficient; * Pearson correlation; ‡ Spearman correlation

Discussion

This study, to the best of our knowledge was the first study in Iraq which investigated the level of anxiety and depression in a sample of patients with hypothyroidism. Based on the study's findings; hypothyroidism was more frequent in women than in men (85% versus 15%). This finding is similar to the results of numerous previous studies both in Iraq and worldwide [4, 5, 22, 23]. In a cross-sectional study in Baghdad, women with hypothyroidism constituted 77.6% of the studied sample [4]. Similarly, in Basrah, 83% of hypothyroid patients were women [5].

The current study' have also shown that even though all the participants were in euthyroid state, there were confirmed cases of anxiety and depression in both study groups (Table 4). Similarly, other researchers have also reported that hypothyroid patients had mood symptoms in spite of the treatment with levothyroxine and the achievement of euthyroidism [12, 13]. There are different explanations for the anxiety and depression in hypothyroid patients. According to "hypothyroid brain" theory, alterations and disruptions of the mood in these patients could be the consequence of a state of local hypothyroidism in the brain, although the peripheral thyroid hormone levels are normal [24,25]. This disruption in mood and health status could also be the result of patients' knowledge of their diagnosis with thyroid disorder [3,26]. Factors other than hypothyroidism which could influence mood symptoms in the participants could also include social conditions and stressful life events.

The current study has shown non-significant differences in anxiety and depression scores between patients receiving a low dose of levothyroxine and those receiving a high dose of levothyroxine. This could indicate non-significant effect of the dose magnitude on anxiety and depression symptoms. A study has also found non-significant differences in quality of life, mood and cognition of hypothyroid patients who were randomly assigned to receive different doses of levothyroxine to attain three ranges for TSH level (low normal, high normal and mild elevated range) [27].

On the other hand, a cross- sectional study has indicated that minor reduction in health status and mood was found in patients receiving replacement or TSH-suppressive doses of levothyroxine [(26)].

With regard to the patients' clinical characteristics, non-significant correlations with anxiety and depression scores were observed, (Table 5). TSH levels were also previously shown to have no correlation with depression scores [(28)]. Also, an online study found no relationship of anxiety and depression scores with levothyroxine dose, duration of the disease, measurement of TSH, free T4 and free T3 levels in women with hypothyroidism [(29)]. In contrast Wu *et al.* who conducted a study in China, found significant association of anxiety and depression scores with free T4, free T3 and TSH levels in patients with autoimmune disease [(30)].

The Limitations of the current study include the relatively small sample size and that it was a cross sectional study which means unavailability of measuring the anxiety and depression scores before starting therapy with levothyroxine and comparing these scores after receiving levothyroxine treatment.

Conclusion

This study has shown that cases of anxiety and depression were reported despite the patients had achieved euthyroid state. However, clinical characteristics did not significantly influence the scores of anxiety and depression. Therefore, it is advisable to ensure that the follow up for hypothyroid patients includes not only assessment of thyroid function tests but also screening for mental disorders like anxiety and depression.

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Conflicts of Interest

The authors declare that there is no conflict of interest

Ethics Statements

The study was approved by the Scientific Committee of the College of Pharmacy/University of Baghdad and Medical City Directorate/Ministry of Health. Verbal consent was obtained from the patients before their enrolment in the study.

Author Contribution

Nada Hamid Rasheed: Data collection, Investigation, Methodology, Formal analysis, Writing – Original Draft Preparation . Basma Zuheir Al-Metwali: Conceptualization, Project Administration, Supervision, Visualization, Writing – Review & Editing . Mohamed Sadoon Mohsen Al Shamaa: Investigation, Methodology, Supervision, Validation, Visualization.

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