

Prevalence of depression in group of hypothyroid patients and its relationship with the level of hypothyroidism.

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Abstract

Background and aims: To study the prevalence of depression among a sample of clinical and subclinical hypothyroid patients, in addition to the correlation between thyroid-stimulating hormone and depression severity.

Study design: A cross-sectional study in Al Mouwasat University Hospital, Damascus, Syria.

Materials and methods: A total of 114 patients diagnosed with hypothyroidism were evaluated by interview using the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria.

Results and conclusion: The prevalence of depression among patients with hypothyroidism (either clinical or subclinical) was 31.57%. Higher depression rates were observed in clinical hypothyroidism patients compared with subclinical hypothyroidism patients. In addition, depression severity was also higher in the clinical hypothyroidism group. Increased rate and severity of depression with increased TSH levels. However, the rate and severity of depression are inversely proportional to the duration of the diagnosis of hypothyroidism.

Keywords: Depression, Hypothyroidism, DSM-5, Syria.

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Introduction

Depression is one of the most common psychiatric disorders with an estimated global incidence of 300 million patients of all ages according to the World Health Organization (WHO) in 2017, affecting women more than men and incidence rates are inversely proportional to age, prevalence rates in life are estimated between 5-17% and annual incidence is 1.59% [1,2].

In addition, to the large prevalence of depression, its importance comes from the large number of morbidities and mortalities which it leads to. Reports show that depression is the leading cause of suicide [3]. Moreover, depression has a major impact on the emergence of disability in daily activities and events, and it is expected to become the second cause of disability after heart disease in early 2020 [1,4,5].

The pathophysiology underlying depression is not clearly defined, and current evidence suggests that several

pathological mechanisms are involved [6]. Furthermore, the main cause of depression is yet not well-known, and as in most psychiatric disorders, depression is caused by a collaboration of multiple genetic and environmental factors [7].

The pathophysiology behind major depressive disorder has not been clearly identified, and current evidence suggests that several pathological mechanisms are involved: 5-hydroxytryptamine (5-HT) central nervous system activity disorder, which is confirmed by the high therapeutic efficacy of Selective Serotonin Uptake Inhibitors (SSRIs) and previous studies have shown severe transient recurrence in depressive symptoms with low levels of Serotonin 5-HT in the central nervous system) [8], also disturbance of the dopamine activity of the central nervous system whether through lack of release from the presynaptic neurons, or a disorder of the post-synaptic receptors by low count or effectiveness, or an intracellular signal disturbance [9].

Moreover, genetic factors play an important role in depression development; studies reported that depression in children may be transmitted from parents through mutation in several genes. Twins-studies showed that the rate of depression in identical twins was 40-50%. The prevalence of depression in first-degree relatives is three times higher than the general population [10].

Most patients with depression appear to have a normal appearance; negligence, lack of hygiene, and weight changes can be observed in more severe depressive conditions. Depression can also be characterized by emotional motor agitation, lack of interaction with the surroundings and lack of emotional expression. On the other hand, speech may be normal, slow or monotonic [11].

Patients usually suffer from low mood, loss of interest or pleasure in activities, and a decrease in energy that leads to fatigue, where it is common to feel exhausted even after the least effort. Other frequent symptoms include sleep disturbances, poor concentration and attention, low self-esteem and self-confidence, feelings of guilt or hopelessness. The patient often has pessimistic looks about the future and may want to hurt himself or commit suicide.

Some depression cases are undiagnosed as the main manifestations of depression in many patients may be physical complaints only, without expressing the other manifestations of depression explicitly by the patient. Physical complaints include non-descriptive structural pain, headache, chronic fatigue, and non-descriptive thoracic or abdominal pain [12]. Clinical depression is diagnosed based on detailed medical history and clinical findings based on (DSM-5) criteria [10]. Neuropsychiatric events are the earliest and most common demonstrations of hypothyroidism, affecting both adults and young adults. In adults, it may cause fatigue, slowness, slow thinking, and mood swings [13].

Many studies have shown that there is a strong relationship between depression and hypothyroidism, both clinical and sub-clinical, as the symptoms of depression may be seen in 40% of patients with clinical hypothyroidism. The correlation between depression and sub-clinical hypothyroidism is more controversial despite the existence of evidence indicating a correlation between depression that is resistant to treatment and sub-clinical hypothyroidism conditions [14,15].

This correlation due to the fact that thyroid hormones are essential in the development of the central nervous system. Brain cells have the largest number of T3 receptors compared to other tissues, especially amygdala and Hippocampus, and the thyroid hormone has a role in maintaining central nervous system stabilization [16]. Previous studies showed that the higher the severity of hypothyroidism, the worse the symptoms of depression [17]. To the best of our knowledge, this is the first study

in Syria aiming to determine the prevalence of depression in hypothyroid patients, both clinical and sub-clinical cases, and its association with hypothyroidism according to DSM-5 diagnostic criteria.

Materials and Methods

A Cross-Sectional Study was conducted in Al Mouwasat University Hospital, Damascus, Syria between August 2015, and November 2016. Patients diagnosed with clinical or subclinical hypothyroidism, those who were clinically stable, were approached for study recruiting. Ethical approval was obtained from the Faculty of Medicine of Damascus University Ethical Committee. Informed Consent was obtained from each recruited participant.

Exclusion criteria included patients: who refused to participate in the study, pregnant and breastfeeding women, alcoholic or using drugs, and who were previously diagnosed with depression by a psychiatrist or being treated with anti-depressive drugs.

After taking the informed consent, demographic data collected included: age, gender, profession, residence (city or rural areas), educational level (with or without higher education), family status, smoking, Body Mass Index (BMI), comorbidities, duration of hypothyroidism and adjuvant drugs. Blood samples were collected and TSH titers were measured using the electro chemiluminescence technique.

Immune Assays: All tests were done in the same lab (Al Mouwasat University Hospital Lab, Damascus, Syria). All tests were done using the same immune assay, these were primarily measured on the instrument Cobas 6000 (Roche Diagnostics) [18]. Reference range was considered as: TSH: 0.45-4.5 uIU/ml, F-T4: 0.8-1.6 ng/dL.

Subclinical hypothyroidism was diagnosed when the patients' TSH is over the reference range and F-T4 is normal and Clinical hypothyroidism is considered when TSH is over the reference range and F-T4 is under the reference range [19].

Depression was evaluated by interview using the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition: DSM-5 of major depressive disorder. After diagnosing depression in patients who met the diagnostic criteria, it was classified as mild, moderate, and severe [13]. Statistical analysis was done using the Statistical Program for Social Sciences (Version 25; SPSS Inc., Chicago, IL, USA). The value of $P < 0.05$ was considered statistically significant.

Results

Patient's characteristics

The study sample included 114 patients, 107 females (93.9% of the total sample) and 7 males (6.1%). The mean age of the study sample was 41.4 ± 11.1 years.

The study sample was included 23 single patients (20.2%)

and 91 married patients (79.8%). The study sample was distributed according to the smoking habit to 75 non-smokers (65.8% of the total sample) and 39 smokers (34.2% of the total sample). The study sample was distributed according to BMI to 18 patients with normal BMI (15.8%), 77 patients with overweight (67.5%) and 19 patients with obesity (16.7%), with the mean BMI value of the total sample 27.62 ± 2.56 .

According to the level of education, 49 patients did not attend university (43%) and 65 patients completed their university study (57%). The study sample was divided according to career into 52 unemployed participants (45.6%, all females), 33 employees (28.9%), 10 university students (8.8%), and 19 other careers (16.7%, distributed between teacher, pharmacist, doctor, nurse ...). According to the current place of residence, 79 patients living in cities (69.3%) and 35 patients living in rural areas (30.7%).

Participants' were classified according to the presence of Comorbidities into two groups: the first did not contain any disease (isolated Hypothyroidism), included 95 patients (83.3% of the total sample), and the second with Comorbidities included 19 patients (16.7% of the total sample). The Comorbidities were as follows: 11 patients with isolated arterial hypertension (57.9%), 4 patients with isolated diabetes (21.1%) and 4 patients with both arterial hypertension and diabetes (21.1%). Patients' characteristics are summarized in Table 1.

Table 1. Patients' characteristics.

		n (%)
Gender		
	Male	7 (6.1%)
	Female	107 (93.9%)
Age (years)		
0.215		
Marital status		
0.215		
	Single	23 (20.2%)
	Married	79.8 (91%)
Smoking		
	No	75 (65.8%)
	Yes	39 (34.2%)
BMI (kg/m ²)		
0.215		
	Normal BMI	18 (15.8%)
	Overweight	77 (67.5%)
	Obese	19 (16.7%)
Education		
	without higher education	49 (43%)
	with higher education	65 (57%)

Occupation		0.215
	Unemployed	52 (45.6%)
	Employed	33 (28.9%)
	Student	10 (8.8%)
	Other	19 (16.7%)
Residence		
	City	35 (30.7%)
	Rural areas	79 (69.3%)
Comorbidities		0.215
	No	95 (83.3%)
	Yes	19 (16.7%)
Comorbidity Illness		0.215
	Hypertension	11 (57.9%)
	Diabetes Mellitus	4 (21.1%)
	Both	4 (21.1%)

According to the DSM-5 scale, 31.6% of patients throughout the total study sample had depression, while 68.4% of patients did not meet depression diagnostic criteria. There was no statistical difference in the prevalence of depression among the male and female groups ($P=0.064$).

The mean age of the group of patients with depression was 39.78 years, while the mean age of the non-depressed group was 42.22 years, with no statistical difference observed ($P=0.278$). BMI in depressed patients with hypothyroidism was lower than in non-depressed patients with hypothyroidism ($P=0.042$).

The prevalence of depression in the group of patients without higher education was higher than in the group of patients with university education in the study sample (57.1%, 12.3% respectively, $P=0$). Higher depression rates were observed in unemployed patient (55.8%), compared with employed (9.1%), students (20.0%) and other careers (10.5%), with statistical significance ($P=0$). Additionally, patients who lived in the city had a greater depression rate than in the group of patients who live in the countryside (40.5%, 11.4% respectively, $P=0.002$).

The prevalence of depression in patients with other comorbidities was 21.1%, while in patients who did not have any other comorbidities were 33.7%. With no statistically significant difference ($P=0.280$). The association of depression with patients' characteristics are summarized in Table 2. The study sample was classified by type of hypothyroidism to clinical hypothyroidism including 62 patients (54.4%) and sub-clinical hypothyroidism including 52 patients (45.6%). 63.89% of patients have a mild degree of depression, 33.34% of patients have a moderate degree of depression, while only 2.7% have severe depression.

Table 2. Depression diagnosis association with patients' characteristics.

		Total	No depression n (%)	Depression n (%)	P-value
Depression		114	78 (68.4%)	36 (31.6%)	
Age (years)		41.4 ± 11.1	42.22	39.78	0.278
BMI (kg/m ²)		27.62 ± 2.56	27.96 ± 2.61	26.91 ± 2.32	0.042
Education					
	Without higher education	49	21 (42.9%)	28 (57.1%)	
	with higher education	65	57 (87.7%)	8 (12.3%)	
Occupation					
	Unemployed	52	23 (44.2%)	29 (55.8%)	
	Employed	33	30 (90.9%)	3 (9.1%)	
	Student	10	8 (80.0%)	2 (20.0%)	
	Other	19	17 (89.5%)	2 (10.5%)	
Residence					0.002
	City	35	47 (59.5%)	32 (40.5%)	
	Rural areas	79	31 (88.6%)	4 (11.4%)	
Comorbidities				0.28	Unemployed
	No	95	63 (66.3%)	32 (33.7%)	
	Yes	19	15 (78.9%)	4 (21.1%)	

When classifying hypothyroidism to clinical and subclinical, we found that the prevalence of depression in the group of patients with clinical hypothyroidism was greater than in the group of patients with subclinical hypothyroidism (P=0.001). All subclinical hypothyroidism patients had mild levels of depression, while 51.85% of clinical hypothyroidism had mild depression and 44.45% had a moderate level of depression and 2.7% (one patient) had severe hypothyroidism.

The average duration of hypothyroidism was two years. The duration of hypothyroidism in the non-depressed group was greater than in the group of people with depression (P=0.000). The higher the duration of hypothyroidism, the lower the severity of depression.

There is a statistically significant moderate correlation between the severity of depression and the duration of hypothyroidism (years) (P=0, r=-0.46). The Mean of TSH for the entire study sample was 17.09 mm/l. TSH concentration mean was lower in the group of people without depression (P=0.000). High TSH concentration levels are associated with a high degree of depression. There is a statistically significant moderate correlation between the severity of depression and TSH concentration levels (P=0.000, r=0.581). Additional characteristics of hypothyroidism and its relation to depression are summarized in Table 3.

Discussion

The prevalence of depression patients with hypothyroidism (either clinical or subclinical) is found to be 31.57%. Previous studies reported a percentage of 22-65% [15,20]. When classifying hypothyroidism to clinical and subclinical hypothyroidism, depression was diagnosed in

17.3% of subclinical hypothyroidism and 43.5% of clinical hypothyroidism patients. This shows that depression is one of the most symptoms of hypothyroidism and is found in even subclinical hypothyroidism [18].

In our cohort, we found that the prevalence of depression in patients with clinical hypothyroidism was greater than the group of patients with subclinical hypothyroidism. In addition, we found that higher TSH concentrations are associated with higher depression rates. On the other hand, fewer depression rates were observed when the duration of hypothyroidism diagnosis was longer.

This association of depression with hypothyroidism was reported previously [15,20-24]. Although other studies did not support this association [19, 25-29]. This contrasting result could be attributed to several factors: the number of subjects enrolled, methods or criteria used to diagnose depression and thyroid assessment based on sing basal TSH and Free T4 test [30-32].

Table 4 includes a literature review and a comparison between relevant studies. It is noted from the previous table that all the presented studies found a relationship between hypothyroidism and depression, but they varied in the importance of the effect of both the duration and severity of hypothyroidism on depression. The study included 114 patients (107 females and 7 males) with diagnosed hypothyroidism, this may be attributed to the fact that most of the patients diagnosed with hypothyroidism are females [19]. The study was conducted at Al Mouwasat University Hospital which is one of the main referral hospitals in Damascus City, Syria. This study is one of the clinical studies that aimed to focus on depression as one of the most important clinical manifestations seen in the context of hypothyroidism.

Table 3. Characteristics of hypothyroidism and its relation to depression.

Yes	No depression	Mild	Moderate	Severe	Total	Pearson's Correlation
Clinical hypothyroidism - n (%)	35 (56.5%)	14 (22.6%)	12 (19.4%)	1 (1.6%)		
Subclinical hypothyroidism - n (%)	43 (82.7%)	9 (17.3%)	0 (0%)	0 (0%)		
Total - n (%)	78 (68.42%)	23 (20.17%)	12 (10.52%)	1 (0.87%)		
Duration of hypothyroidism (years) (mean ± SD)	2.57 ± 3.00	0.68 ± 1.03			2 ± 2.7	r=-0.46
TSH concentration (uIU/ml)	9.90 ± 4.22	32.65 ± 53.82			17.08 ± 19.88	r=0.581

Table 4. A literature review and a comparison between relevant studies.

Study	Country	Sample Size	Depression Scale	Sample Characteristics	Correlation between depression and hypothyroidism	Hypothyroidism duration and depression	Hypothyroidism severity and depression
Hamed et al., (Current Study)	Syria	140	DSM-V	m and f, 18-75 yrs, with clinical and subclinical hypothyroidism	31.6% of the sample had depression (no difference observed between m and f)	SS	SS
Manish et al., [15]	India	100	HDRS	m and f, 19-90 yrs, with clinical and subclinical hypothyroidism	60% with depression (56% m, 65% f)	NA	SS
Ittermann et al. [24]	Germany	500	GHQ-30	m and f, 15-60 yrs with clinical and subclinical hypothyroidism	29.6% had depression	SS	NA
Demartini et al. [20]	Colombia	123	DSM-IV	m and f, 18-70 yrs, with subclinical hypothyroidism	63% had depression symptoms, 18% had depression episodes	NA	NSS
Nellyc et al. [37]	Mexico	150	DSM-IV	f, 15-65 yrs, with clinical hypothyroidism	25% had depression	SS	SS
Tomsen et al. [38]	Denmark	165000	HADS	m and f, 25-85 yrs, with clinical and subclinical hypothyroidism	46% had depression	SS	SS
Juha et al. [19]	Finland	2896	BDI-21	m and f, 45-74 yrs, with clinical and subclinical hypothyroidism	25% had depression (22.5% m, 27.5% f)	SS	SS
Engum et [26]	United States	6869	HADS	m and f, 20-60 yrs, with clinical and subclinical hypothyroidism	33.6% had depression	NA	NA

Depression symptoms were measured about 2 years after the diagnosis of hypothyroidism when might suggest that thyroid disorders may be an antecedent of depression, this was also reported previously [24] as depression is more obvious in newly diagnosed patients. This may be credited to the fact that those patients were not treated with levothyroxine compared with patients diagnosed

from long ago, although levothyroxine treatment for patients with chronic hypothyroidism was not sufficient, it has contributed in the reduction of depression incidence and severity. An interaction of TSH with T4 intake on depression was suggested previously, this also suggests that the association between TSH and depression might be moderated with T4 intake [24,29].

Additionally, a previous study from Taiwan reported that hypothyroidism may be also a manifestation of depression, as incidence rates of hypothyroidism were higher in patients with depression compared with controls [24,33]. We could explain the high prevalence of depression in the study participants due to hypothyroidism effects on the central nervous system. Decreased levels and efficacy of serotonin in the brain as well as the reduced response for catecholamines, the reduced glucose uptake in the brain, the reduced activity of D2 enzyme which converts T4 to the active T3 in the brain, the reduced metabolic activity in the brain in addition to the possibility of diminished brain perfusion in hypothyroidism patients were demonstrated in these patients [13-17]. Another explanation is that hypercortisolism which is more observed in depression might lead to changes in the hypothalamic-pituitary-thyroid axis [34,35]. The study shows that the rate of depression increased with higher TSH levels, despite the fact that previous population-based reports found the opposite results [16,19,24,37]. The different results between our study and previous reports may be attributed to different time points between depression and hypothyroidism diagnosis (which is about 2 years in our study and 1-5 years as previously reported) [24].

We recommend the Investigation of the presence of depression in patients with hypothyroidism should be among the routine investigation of the disease, especially in patients who have a higher risk of depression to establish the diagnosis and early treatment of the condition. moreover, other studies can be conducted later that include a greater number of patients and clarify the effect of depression on the quality of life in patients with hypothyroidism using special data, also can study the effect of depression treatment in improving the quality of their lives and their symptoms [37,38].

Study Limitations

The study is a cross-sectional study, not case-control which is a statistically stronger study.

Conclusion

The present study found that the prevalence of depression among patients with hypothyroidism (either clinical or subclinical) was 31.57%. Higher depression rates were observed in clinical hypothyroidism patients compared with subclinical hypothyroidism patients. Moreover, depression severity was also higher in the clinical hypothyroidism group.

Author Contributions Statement

RT and YL design the study, RT collected the data, AH, NN and NA conducted the statistical analysis, AH, NN and drafted the initial manuscript, All authors revised the final version of the article and approved it for final publication.

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