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Unexplained Somatic Symptoms due toDepression and/or Subclinical Hypothyroidism

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Abstract

Background: Unexplained somatic symptoms are common presentation of many diseases including subclinical hypothyroidism and depression. Subclinical hypothyroidism (mild thyroid failure) represents an early stage of thyroid disease that will commonly progress to overt hypothyroidism.

Objectives: To assess the presence of depression and subclinical hypothyroidism (mild thyroid failure) in patients presenting with unexplained somatic symptoms aiming for better care provided to those patients. Special care should be provided to females as they are more likely to be affected by both conditions.

Method: Patients were collected conveniently from those attended internal medicine clinic during the period from January to August 2013 complaining from multiple unexplained somatic symptoms. Patients with clinical hypothyroidism or anemia or other cause of their presenting somatic complaints were excluded from the study. Remaining 48 patients were having only unexplained somatic symptoms which proved after investigation to have subclinical hypothyroidism with high TSH while their T4 were normal. Then they were screened for depression byPatient Health Questionnaire 9 (PHQ-9), fatigue severity scale (FSS), Somatic Symptom Inventory (SSI), and Sheehan Disability Scale (SDS) for measurement of functional impairment.

Results: Females (n=36) represent 75% of cases while males (n=12) represent only 25% of cases. FSS was significantly higher in females than males (t=2.373, p=0.023). Fatigue is the most common presenting symptom among all patients (n=21, 43.7%) followed by weight gain (n=16, 33.3%)
and lastly generalized aches (n=11, 22.9%). More females presented with fatigue (n=15, 72.7%) than males (n=6, 28.6%). Females are earlier than males to seek medical advice. Only 19 patients (39.6%) were presented early and females were majority of them (n=17, 89.5%). There were positive correlations between severity of depression and (physical symptoms severity, fatigue, and degree of functional disability). There were significant negative correlations between T4 serum level and (depression severity and degree of functional disability).

Conclusion: Mild thyroid failure frequently progresses to overt hypothyroidism. It may clearly be associated with somatic symptoms, depression, memory and cognitive impairment. It is common more in females than males regardless their age. Early detection & treatment of mild thyroid failure and depression has been reported to be cost-effective and can prevent further functional impairment.

Introduction

Primary care physicians, not mental health professionals, treat the majority of patients with symptoms of depression. Persons who are depressed have feelings of sadness, loneliness, irritability, worthlessness, hopelessness, agitation, and guilt that may be accompanied by an array of physical symptoms (1, 2). Recognizing depression in patients in a primary care setting may be particularly challenging because patients, especially men, rarely spontaneously describe emotional difficulties. On the contrary, patients with depression who present to a primary care physician often describe somatic symptoms such as fatigue, sleep problems, pain, loss of interest in

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sexual activity, or multiple, persistent vague symptoms (3)

Subclinical hypothyroidism (mild thyroid failure) is defined as an elevated serum TSH level associated with normal total or free T_4 and T_3 values. The overall prevalence has been reported to range from 4–10% in large general population screening surveys (4).

Mild thyroid failure represents an early stage of thyroid disease that will commonly progress to overt hypothyroidism. Progression has, in fact, been reported to occur in approximately 3–18% of affected patients per year (5). One study evaluated the natural history of mild thyroid failure in 154 female patients over a 10-yr period; 57% of patients continued to have mild thyroid failure, 34% of patients progressedto overt hypothyroidism, and 9% of patients reverted to a normal TSH level (5).

The laboratory profile of an elevated serum TSH and normal free thyroid hormone levels really represents "compensated hypothyroidism." The affected subject is really euthyroid because the increased TSH is stimulating and driving the thyroid gland to produce normal thyroid hormone levels. Certainly, elevated serum TSH levels do stimulate even a diseased thyroid gland to produce and release more thyroid hormone (6).

However, as long as the serum TSH level remains elevated, the thyroid hormone levels are not truly normal for that individual. The clearance kinetics of thyroid hormones and TSH from the circulation actually make such a conclusion inescapable. Because the half-life of T_4 is 7 day and that of T_3 is 1 day, the serum TSH, which has a half-life of less than 1 hour, would certainly be expected to return to normal if thyroid hormone levels were, indeed, normal for that individual. An elevated TSH in an individual patient, thus, means that the circulating thyroid hormone concentrations are insufficient, with a few rare exceptions (TSH-secreting tumors) (6).

Unexplained somatic symptoms are more common in females (7). Major depression is 2-3 times more common in females than males (8). Also subclinical hypothyroidism is more common in females than males (9).

Hypothesis: presence of unexplained somatic symptoms can denote underlying depression or subclinical hypothyroidism or both. These conditions if treated early can prevent further functional impairment.

Aim of the study is to assess the presence of depression and subclinical hypothyroidism (mild thyroid failure) in patients presenting with unexplained somatic symptoms aiming for better care provided to those patients and early diagnosis and treatment of both depression and mild thyroid failure before it will progress to clinical hypothyroidism or overt depression as both conditions can present with unexplained somatic complaints. Special care should be provided to females as they are more likely to be affected by both conditions.

Patients and methods:

Patients were collected conveniently from those attended internal medicine clinic during the period from January to August 2013 complaining from multiple unexplained somatic symptoms. Only48 patients out of 120 patients proved to have subclinical hypothyroidism or depression as a clinical diagnosis, patients with clinical hypothyroidism or anemia or other cause of their presenting somatic complaints were excluded from the study. Those 48 patients were having only unexplained somatic symptoms which proved after investigation to have subclinical hypothyroidism with high TSH while their T4 were normal (TSH: normal range between 0.46 and 4.68mIU/L&Free T4: normal range between 10 and 28p mol/L).

Patient Health Questionnaire 9 (PHQ-9): 9 item self report scale designed to screen for depression in primary care. It represents depression subscale of patient health questionnaire. It assesses the depressive symptoms as defined by DSM-IV over the previous 2 weeks, and containing one question concerning functional impairment. The scale is useful as a screening tool for depression. Item 1-9 are scored from 0-3. Scores from 1-4 indicate minimal depression, 5-9 mild depression, 10-14 moderate depression, 15-19 moderately

severe depression, 20-27 severe depression (10).

Fatigue Severity Scale (FSS): this scale developed originally to assess fatigue in multiple sclerosis and other related conditions. The scale was specifically designed to differentiate fatigue from clinical depression. Items are scored on a 1-7 scale, with higher score (range 7-63) indicating greater severity of fatigue (11).

Somatic Symptom Inventory (SSI): 26 items assessing severity of somatic Symptomatology, body sensations and overall health. The scale is used primarily as a measure of hypochondriasis and severity of somatic symptoms. Items are scored on a 1 (not at all) to 5 (a great deal) scale with a total score range from 26-130 (12).

Sheehan Disability Scale (SDS): is a brief 3- item self report inventory designed to assess the degree to which symptoms of panic, anxiety, depression or phobia have disrupted the patient's work, social life and family life. It is a brief and easy measure to assess disability. All items are scored on a 0-10 scale, where 0 represents no impairment, 1-3 mild impairment, 4-6 moderate impairment, 7-9 marked impairment, 10 extreme impairment. The 3 primary items can be summed into a single measure of global impairment (range 0-30). Scores > 5 on any of the subscles are indicative of functional impairment and increased risk of mental disorder (13).

Statistical methods:

IBM SPSS statistics (V. 21.0, IBM Corp., USA, 2012) was used for data analysis. Data were expressed as Mean±SD for quantitative parametric measures in addition to Median Percentiles for quantitative non-parametric measures and both number and percentage for categorized data.

The following tests were done:

1. Comparison between two independent mean groups for parametric data using Student t test.
2. Comparison between two independent groups for non-parametric data using Wilcoxon Rank Sum test.
3. Comparison between more than 2 patient groups for parametric data using Analysis of Variance (ANOVA).

The multiple comparisons (Post-hoc test or least significant difference, LSD) was also followed to investigate the possible statistical significance between each 2 groups.

4. Comparison between more than 2 patient groups for non-parametric data using Kruskall Wallis test.
5. Pearson correlation test to study the possible association between each two variables among each group for parameteric data.
6. Chi-square test to study the association between each 2 variables or comparison between 2 independent groups as regards the categorized data.

The probability of error at 0.05 was considered sig., while at 0.01 and 0.001 are highly sig.

Results

Table (1): Descriptive Statistics:

	n	Min.	Max.	Mean	SD
Age	48	20	58	39.313	10.3063
TSH	48	4.7	10.7	6.695	1.5438
T4	48	11	18.7	12.088	1.95792
PHQ	48	6	30	17.833	5.22
SSI	48	39	117	80.5	17.3426
FSS	48	13	59	26.188	9.6704

TSH (thyroid stimulating hormone), T4 (free T4), PHQ (Patient Health Questionnaire), SSI (Somatic Symptom Inventory), FSS (Fatigue Severity Scale). Females (n=36) represent 75% of cases while males (n=12) represent only 25% of cases.

Table (2): Gender difference in all variables measured

	Females n=36		Males n=12	
	mean	SD	mean	SD
Age	38.583	9.524	41.5	12.5806
TSH	6.8419	1.47557	6.2542	1.72418
T4	12.0947	1.86179	12.0667	2.31294
PHQ	18.583	4.9591	15.583	5.5507
SSI	82.389	18.3945	74.833	12.7196
FSS	27.611	10.3296	21.917	5.7912

Student t Test: It was done for comparison between females and males with no significant statistical difference between them except for FSS (t=2.373, p=0.023). There were 43 married patients and only 5 single patients with no statistically significant difference between them except that the age of single pts was younger than that of married.

Table (3): assessment of variables in patients according to the presenting complaint; Analysis of variance (ANOVA):

	Generalizedaches n=11		Malaise n= 21		Weight gain n=16		f	P
	mean	SD	mean	SD	mean	SD		
Age	36.8	9.331	38.143	9.331	43.5	11.095	1.864	0.167
TSH	6.674	1.3264	6.5471	1.5388	6.8894	1.7838	0.212	0.81
T4	12.791	2.9773	11.8905	1.8121	11.9	1.3743	0.801	0.455
PHQ	19.8	5.1812	17.571	5.9462	16.875	4.2876	0.984	0.382
SSI	86.5	10.319	79.857	18.443	78.688	19.401	0.68	0.512
FSS	26	7.0553	27.571	10.738	26.149	10.154	0.476	0.624

There was no significant statistical difference between patients regarding thepresenting complaints they came with.

Table (4): gender difference in distribution of presenting symptoms

Presenting symptom among 48 patients		Females (n=36) 75% of cases		Males (n=12) 25% of cases		Z test	P value
		number	%	number	%		
Generalized aches		8	72.7	3	27.3		
N=11	22.9%					0.1983	>0.05
Malaise (fatigue)		15	71.4	6	28.6		
N=21	43.7%					0.504	>0.05
Weight gain		11	68.7	5	31.3		
N=16	33.3%					0.7071	>0.05

No significant statistical difference between females and males regarding the presenting symptoms. Fatigue is the most common presenting symptom among all patients (n=21, 43.7%). More females presented with fatigue (n=15, 72.7%) than males (n=6, 28.6%).

Table (5):gender difference regarding time of presentation

Time elapsed before clinical presentation		Females n=36		Males n=12		Z test	P value
		Number	%	Number	%		
Early presentation (weeks)		17	89.5	2	10.5		
N=19	39.6%					1.8745	<0.05
Late presentation (months)		18	62.1	11	37.9		
N=29	60.4%					2.5561	<0.01

Females usually come early after few weeks of illness, while males are reluctant to come except late. Only 19 patients (39.6%) were presented early and females were majority of them (n=17, 89.5%, $p<0.05$). Even in late presentation females are significantly more keen to seek medical advice (n=18, 62.1%, $p<0.01$).

Pearson Correlation Test:

There was no correlation between age of patients and scores on PHQ, SSI, FSS, Sheehan DS, TSH or T4.

There was highly significant positive correlation between scores of patients on PHQ and their scores on SSI ($r = 0.574$, $p = 0.000$), FSS ($r = 0.544$, $p = 0.000$) and Sheehan DS ($r = 0.488$, $p = 0.000$).

There was highly significant negative correlation between scores of patients on PHQ and their T4 level ($r = -0.409$, $p = 0.004$).

There was highly significant positive correlation between scores of patients on SSI and their scores on FSS ($r = 0.636$, $p = 0.000$) and Sheehan DS ($r = 0.582$, $p = 0.000$).

There was statistically not significant negative correlation between T4 level and scores of patients on SSI ($r = -0.214$, $p = 0.144$) and also FSS ($r = -0.216$, $p = 0.141$).

There was significant negative correlation between scores of patients on Sheehan DS and their T4 level ($r = -0.292$, $p = 0.044$).

Discussion

Depression is the second most common chronic disorder seen by primary care physicians on average, 12 percent of patients seen in primary care settings have major depression (14). The degrees of suffering and disability associated with depression are comparable to those in most chronic medical conditions (15). Fortunately, early identification and proper treatment significantly decrease the negative impact of depression in most patients (16, 17).

Targeted screening in high-risk patients such as those with chronic diseases, pain, unexplained symptoms, stressful home environments, or social isolation, may provide an alternative approach to identifying patients with depression (1).

In our study, we examined 120 patients who attended the internal medicine clinic complaing of unexplained somatic symptoms. Out of those patients only 48 patients proved to have subclinical hypothyroidism as a clinical diagnosis. The rest of patients were having clinical hypothyroidism or anaemia or other cause of their presenting somatic complaints. Those patients were excluded from the study. Those 48 patients were having only unexplained somatic symptoms which proved after investigation to have subclinical hypothyroidism with high TSH while their T4 were normal. Patients were screened for depressive symptoms, fatigue severity, other somatic complaint, and functional disability.

Consistent with The Colorado Thyroid Disease Prevalence Study (18) measured serum TSH levels and conducted symptom surveys in over 25,000 state residents. Elevated serum TSH values were found in 9.5% of all subjects and in 8.9% of those who were not already on thyroid hormone therapy; 75% of these individuals had serum TSH levels in the 5–10 μU/ml range. In response to a validated survey regarding symptoms of thyroid hormone deficiency, the 2,336 subjects who were identified as having mild thyroid failure significantly more often reported having dry skin (28%), poor memory (24%), slow thinking (22%), muscle weakness (22%), fatigue (18%), muscle cramps (17%), cold intolerance (15%), puffyeyes (12%), constipation (8%), and hoarseness (7%) than did euthyroid subjects. It is important to note that, whereas euthyroid subjects experienced a mean of12.1% of all listed symptoms, overtly hypothyroid subjects had 16.6% of these symptoms ($P < 0.05$ *vs*. euthyroid group), and subjects with mild thyroid failure reported an intermediate 13.7% of the symptoms ($P < 0.05$ *vs*. euthyroid group). This suggests a "dosage effect" between levels of thyroid hormones and symptoms.

Consistent with these findings, a Swiss study involving 332 women with hypothyroidism reported that 24% of the 93 subjects with mild thyroid failure exhibited typical symptoms of hypothyroidism (19)

Descriptive Statistics of our study: patients age range from 20-58 with mean age of 39.31, standard deviation (SD) 10.30. TSH levels range from 4.7 to 10.7 IU/L (TSH: normal range between 0.46 and 4.68mIU/L), mean level (6.69), SD (1.54). Free T4 level ranges from 11-18.7(normal range between 10 and 28p mol/L), mean level (12.08), SD (1.95). Patient health questionnaire scores range from 6-30, with mean score 17.8 and SD 5.22. Symptom severity inventory score ranges from 39-117 with mean (80.5) and SD (17.34). Fatigue severity scale score ranges from 13-59 with mean score (26.18), SD (9.67).For each of those questionnaires; the higher score represent more impairment severity. There were 36 females and 12 males with no statistically significant difference between males and females regarding age or other scales measured except for fatigue severity scale; females were higher (27.61, SD=10.32) than males (21.31, SD=5.79) with student t test ((t=2.373, p=0.023). There were 43 married patients and only 5 single patients with no statistically significant difference between them except that the age of single patients was younger than that of married. Fatigue is the most common presenting symptom among all patients (n=21, 43.7%). More females presented with fatigue (n=15, 72.7%) than males (n=6, 28.6%).Females

are more likely to come early after few weeks of illness, than males (17 compared to 2).

This is consistent with the finding that subclinical hypothyroidism is more common in women than men, and its prevalence increases with age (9). Also gender differences in somatic scores were very small. Thus, differences in the experience and reporting ofsomatic symptoms would not likely explain gender differences in depression rates and symptom severity (7).Women are 2–3 times more likely to experience Major Depressive Disorder (MDD) than men (8) and have higher scores on self-report depression symptom measures (20). Similarly, women are more likely to be diagnosed with other psychiatricdisorders that involve physical symptoms, including somatoformdisorders (21). Some of the symptoms of these disorders overlap substantially with symptoms of MDD. Women may also more frequently report other physical symptoms potentially related to emotional distress (e.g., headache, back pain) than men (22).

In our study, it was found that there was no correlation between age of patients and scores on PHQ, SSI, FSS, Sheehan DS, TSH or T4. Meaning that age is not the variable that affect the severity of symptoms, depression, or thyroid functioning.There was highly significant positive correlation between scores of patients on PHQ and their scores on SSI (r =0.574, p = 0.000).Meaning that symptoms severity increase with the increase in score of depressive symptoms.

This is consistent with a cross-sectional, nationwide epidemiologic study, carried out in 1150 primary care patients with depression, disability associated with somatic symptoms and number of somatic symptoms was strongly associated with increased depression severity and health resources utilization (23)

In our study ,there was highly significant positive correlation between scores of patients on FSS and their scores on PHQ (r =0.544, p = 0.000) and also Sheehan DS (r =0.523, p = 0.000).This means fatigue symptoms severity increase with the increase of depressive symptoms score and also there will be increase in their functional disability.There was highly significant positive correlation between scores of patients on PHQ and their scores on Sheehan DS (r =0.488, p = 0.000).Meaningthat; the degree of patient functional disability increases with the increase of depressive symptoms scores. There was highly significant positive correlation between scores of patients on SSI and their scores on FSS (r =0.636, p = 0.000) and also Sheehan DS (r =0.582, p = 0.000).Meaning that the higher the symptoms severity score; the higher will be the fatigue severity score will be and also the higher will be their functional disability.

This is consistent with a finding that fatigue is not only a symptom of depression but also one of the most common residual symptoms of a partially resolved depression. Broadly defined, symptoms of fatigue can affect physical, cognitive, and emotional function, impair school and work performance, disturb social and family relationships, and increase healthcare utilization (24).

In our study, there was highly significant negative correlation between T4 serum level and their PHQ score(r = -0.409, p = 0.004) and also Sheehan DS (r = -0.292, p = 0.044). Meaning that the lower the T4 serum level; the higher the depressive symptom score and functional disability will be and vice versa.

These result are consistent with another study where it was found that depression was more frequently present among individuals with subclinical (74/149 = 49.7%) hypothyroidism than among individuals with overt hypothyroidism (21/125 = 16.8%&$p < 0.001$). Indeed, subclinical hypothyroidism increased the risk for a patient to present depression more than four times (OR = 4.886; 95% confidence interval = 2.768–8.627).These results demonstrate that subclinical hypothyroidism increases the risk for depression (25).

In our study, there was statistically no significant negative correlation betweenT4 level and scores of patients on SSI (r = -0.214, p = 0.144) FSS (r = -0.216, p =

0.141). Meaning that the lower the level of T4 the higher the symptoms severity and fatigue severity scale score will be.

Other cross-sectional studies have demonstrated evidence of specific neurobehavioral and neuromuscular dysfunction in mild thyroid failure patients (26), depression, memory loss, cognitive impairment and a variety of neuromuscular complaints have all been reported to occur more frequently in patients with this condition (27).

Screening for thyroid functions and depression should be done for any patient presenting with unexplained somatic symptoms. This will help for early detection and management of both conditions before further increase in severity and functional impairment. There have been some randomized controlled trials (RCT) examining the effects of L-thyroxine treatment on general symptoms in subjects with mild thyroid failure. It was reported that mild thyroid failure subjects who were treated with L-thyroxine had significantly greater improvement in general hypothyroid symptom scores than did subjects who were treated with placebo (28). One uncontrolled study also reported a reduction of general somatic complaints after L-thyroxine treatment was instituted (29).

Also according to (American association of clinical Endocrinology); the diagnosis of subclinical hypothyroidism must be considered in every patient with depression (30).

Conclusion: Mild thyroid failure frequently progresses to overt hypothyroidism. It may clearly be associated with somatic symptoms, depression, memory and cognitive impairment. It is common more in females than males regardless their age. Early detection & treatment of mild thyroid failure and depression has been reported to be cost-effective and can prevent further functional impairment.

Recommendations

Special care should be provided to females complaining of unexplained somatic symptoms especially fatigue. Those females should be screened for both depression and subclinical hypothyroidism and to be treated accordingly as early as possible.

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