Hypothyroid Symptoms in Levothyroxine-Treated Patients

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ABSTRACT

***Purpose**: Approximately 15% of patients with hypothyroidism are dissatisfied with their treatment due to persistence of residual symptoms associated with hypothyroidism. The purpose of this study was to compare thyroid symptoms using the hypothyroid symptom scale (HSS) in patients receiving stable thyroid therapy for 6 months to patients without hypothyroidism. The HSS was used to identify the percentage of levothyroxine-treated hypothyroid patients with residual or persistent hypothyroid symptoms.*

***Methods**: Patients included in the study had hypothyroidism and were receiving a stable/maintenance dose of levothyroxine sodium therapy, unchanged for at least 6 months. A control group of patients were included if they did not have an active prescription for thyroid hormone therapy. The HSS was administered via phone or face-to-face interactions. Patients were asked to score 10 symptoms over the past month on a scale of 0 to 4 (e.g., 0, absence of, to 4, severe symptoms). Results were analyzed using descriptive and inferential statistics. T-tests and chi-squared analysis were used to assess differences in continuous and categorical variables.*

***Results**: A total of 68% of the contacted patients responded to the survey. A total of 302 patients were in the intervention group and 273 were in the control group. The mean total HSS scores between groups were significantly higher in the treatment compared to the control group (13.92 ± 10.91 vs.10.07 ± 7.85; P < 0.001).*

***Conclusion**: Significantly more patients receiving thyroid hormone therapy experienced residual thyroid symptoms compared to control patients. Attempts should be made to offer alternatives for hypothyroid patients with persistent symptoms.*

Keywords: hypothyroidism, Hypothyroid Symptom scale, residual symptoms

INTRODUCTION

Current estimates indicate that hypothyroidism affects 5%-10% of adult women and 3% of men in the United States (US).[1,2] Overt hypothyroidism in the general population is between 0.3% and 3.7% in the United States and between 0.2% and 5.3% in Europe.[3] The target of therapy is to normalize serum TSH; however, measurement of T3 concentrations may be of greater physiologic importance. There is a large interindividual variability of serum triiodothyronine (T3) levels, as well as, variability in levels with circadian rhythms. Currently, it is unknown if variations in serum triiodothyronine concentrations within the reference range is of physiologic or clinical significance. Normalizing both TSH and T3 concentrations may be important in some situations. Future research should focus on developing more accurate assays to measure serum concentrations of FT3, total T3, and FT4.[4] A recent study by Peterson et al. reported that as many as 15% of treated hypothyroid patients with a normal serum TSH level had approximately 15-20% lower serum T3:T4 ratios in LT4 treatment.[5]

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In the recently published American Thyroid Association (ATA) guidelines for the diagnosis and treatment of hypothyroidism there was a consensus that dosing of levothyroxine should be guided by periodic TSH testing with the goal of therapy to yield levels within the therapeutic range between 0.4 - 4.0 mIU/L. However, there is controversy surrounding this range.[4] Some experts feel that the value should be between 0.4 mIU/L and 2.5 mIU/L.[6] The authors of the guidelines did not recommend changing either levothyroxine doses or formulations of thyroid hormone replacement based upon symptoms.[4,7] There are reports suggesting that normal thyroid function measures are not always indicative of "euthyroidism".[5] Peterson and colleagues found that patients treated with levothyroxine had higher body mass index (despite consuming fewer calories per day).[5] Furthermore, Tan and colleagues evaluated Asian patients receiving levothyroxine replacement therapy in the community setting and found that a decreased quality of life (QOL) score was associated with hypothyroid patients with a single persistent symptom, including weight gain (adjusted OR [95% CI], 3.12 [1.71-5.68]), feeling weak (2.12 [1.09-4.11], and having dry or coarse skin (2.27 [1.24-4.14]), but decreased QOL was not associated with TSH or free thyroxine levels.[8]

Thyroid related symptoms may be subtle and challenging to quantify yet serial measures of such symptoms in patients do support the utility of this approach to patient care.[2,9-13] A previously reported ten Symptom Scale Instrument (Hypothyroid Symptom Scale, HSS) has shown its ability to quantify persistent symptoms in levothyroxine treated

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patients.[11,12] The purpose of this study was to compare thyroid symptoms using the hypothyroid symptom scale (HSS) in patients receiving stable thyroid therapy for 6 months to patients without hypothyroidism. The HSS was used to identify the percentage of levothyroxine-treated hypothyroid patients with residual or persistent hypothyroid symptoms.[13]

METHODS

Study design

Subjects were identified by Proxsys Rx retail pharmacy prescription database in eight health systems between July 2017 and February 2018. Proxsys Rx, is a company that partners with hospital and health systems to fill pharmacy gaps that may exist. The retail pharmacies were integrated inside hospitals to provide bedside delivery and enhance employee benefits through cost savings. Subjects were identified from prescription history at each location. Patients were included in the study if they had hypothyroidism and were receiving a stable/maintenance dose of levothyroxine sodium therapy. Stable/maintenance dose was defined as continuous unchanged levothyroxine sodium therapy for ≥ six months. No serum thyroid measures were evaluated. Patients were excluded if they were receiving any non levothyroxine formulation of therapy. Use of antidepressants, psychoactive medications, statins, and presence of any cardiac disease was recorded.

Proxsys Rx identified patients who met the inclusion criteria based on whether or not patients had an active prescription for levothyroxine for at least six months. A random control group of patients were included who did not have an active prescription for levothyroxine; no thyroid measures were evaluated and patients were not known to have thyroid disease. Patients were not matched on the basis of age or gender. Once identified, eligible patients were contacted by telephone and the HSS was administered between February 3 and June 15, 2018. A script was prepared to assist personnel with maintaining consistency between calls. Responses were recorded in an online tool.[14]

A total of six questions were asked of the patients including whether or not they were currently taking levothyroxine, current use of other medications, current treatment for heart disease, high cholesterol, high blood pressure, mood disorder, or none of these conditions. In addition, patients were asked to complete the HSS to determine whether they experienced the following symptoms over the past month: dry skin, fatigue, weight gain, cold weather intolerance, constipation, muscle stiffness, puffiness, memory loss, feeling blue, or dizziness. The severity of each sign and symptom was rated on a scale from 0 to 4 points with the following numerical designations: absent (0), minimal (1), mild (2), moderate (3), and severe (4). The item scores were totaled to obtain the sum of signs and symptoms, which could range from 0 to 40 points. A HSS score >10 was used to assess residual symptoms as previous reports have shown that the upper limit of total symptoms for normal control subjects was 10.84 +/- 0.75. A copy of the questionnaire is provided in Appendix 1.

The Institutional Review Board of Samford University reviewed and provided the ethics approval for this study, and the study procedures were in accordance with the ethical standard. Participation in the study was voluntary and anonymous. Participants were informed about the purpose and the protocol of the study.

Statistical Analysis

Descriptive statistics were employed to summarize all variables with means and standard deviations presented for continuous variables and frequencies and proportions for categorical variables. T-tests were used to detect differences between two groups for continuous variables. Chi-square tests were used to assess associations between categorical variables. No demographic information was captured with the questionnaire and no analysis was conducted on the basis of demographic information. All analyses were conducted using STATA statistical software package (version 12; StataCorp LP, College Station, TX, USA).

In order to enhance enrollment, the protocol was amended during the recruitment phase to allow for patients to complete a paper-based evaluation that was transcribed into the survey instrument, in addition to the telephonic questionnaire. The amendment was approved by the Samford University Institutional Review Board.

RESULTS

A total of 839 of 999 eligible patients were contacted to generate a random sampling of eligible individuals. A total of 575 patients responded to the survey, yielding a 68% response rate. The treatment group consisted of 302 patients and the control group consisted of 273 patients. Complete data was obtained from 301 patients in the treatment group and 261 patients in the control group. Table 1 displays the distribution of HSS study participants by pharmacy. An independent t-test was used in the sample of responders to determine if there were differences in symptom scores between levothyroxine (the treatment group) patients and the control group. The results are reported in Table 2. The mean HSS scores were significantly higher in the treatment than the control group (13.92 ± 10.91 vs.10.07 ± 7.85; $P < 0.001$). The treatment group had statistically significant higher scores in 9/10 symptoms compared to the control group. The prevalence for the following symptoms were significantly higher in the treatment group compared to the controls: dry skin (P <0.001), fatigue (P <0.001), cold weather intolerance (P <0.01), constipation (P <0.05), muscle stiffness (P <0.05), puffiness (P <0.05), memory loss (P <0.05), feeling blue (P<0.05), and dizziness (P<0.01).

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The distribution of the ten individual symptom items in the control and levothyroxine treated groups, were examined and plotted in Figure 1. Individualized mean scores were higher across all symptoms in the treatment group compared to the control group.

Table 3 shows the proportion of responding subjects with self-reported medication use and comorbidities. Among the responders, self-reported use of medications for comorbidities was higher in the treatment group compared to the control group (80.1% vs. 60.2%; *P* <0.0001), with significant differences in heart disease, high cholesterol, high blood pressure (all *P*-values were <0.0001), but not mood disorder (*P* > 0.05). We determined the percentage of patients in both groups with symptoms score above the average score of controls (10.07). The difference between groups was 20% (64% of the treatment group and 44% of the control group). A total of 192 (63.5%) patients receiving levothyroxine, and 116 (44.4%) patients in the control group had scores > 10 on the HSS. No analysis was conducted to evaluate the impact of concomitant medications and HSS scores in patients with comorbid conditions.

DISCUSSION

The HSS has previously been described and compared to other scoring systems in the clinical assessment of the adequacy of thyroid hormone replacement therapy in patients with hypothyroidism.[15,16] Using this scale, authors of the present study showed that patients treated for hypothyroidism continue to experience significantly more symptoms commonly associated with thyroid disorder compared to patients who have not been diagnosed or treated with levothyroxine for hypothyroidism. This study confirmed the results of a previous one in which patients with hypothyroidism, and who were receiving levothyroxine treatment, were compared with euthyroid patients.[15] In the study by Carle et al., patients with overt hypothyroidism were compared with individually matched control subjects. Patients filled out questionnaires regarding hypothyroid symptoms. Patients with hypothyroidism reported more tiredness (81%), dry skin (63%), and shortness of breath (51%). The highest ORs were reported for tiredness, OR, (5.94 (3.7-9.60), hair loss, OR, (4.58 (2.80-7.51)), and dry skin, OR, (4.09 (2.73-6.16). [15] In the current study, the sum of symptom scores for the control group was 10.07 ± 7.85 vs. 13.92 ± 10.91; *P*<0.001. Singh and colleagues also found that optimal levothyroxine replacement improves symptoms of hypothyroidism. Patients receiving levothyroxine, titrated to a serum TSH range between 0.4 – 4.5 mIU/L, experienced a significant decrease in symptoms (e.g., lack of energy, dry skin, constipation, aches and pains, cold intolerance, poor memory, depression, weight gain, tiredness while walking, and difficulty getting up) after treatment. [17]

Peterson and colleagues evaluated dissatisfaction with hypothyroid therapy in 12,146 patients.[18] Their study reported differences in satisfaction among patients receiving different formulations of thyroid hormones. Patients taking desiccated thyroid extract (DTE) reported a higher median treatment satisfaction of 7 (IQR, 5-9) compared to other treatments. Patients receiving LT4 treatment reported a lower satisfaction score of 5 (IQR 3-7), while those receiving LT4 + LT3 reported a higher satisfaction score of 6 (IQR, 3-8). Patients taking DTE were less likely to report problems related to weight management, fatigue/energy levels, mood, and memory compared to patients taking other agents. The authors suggested that additional studies be conducted to better determine the therapeutic basis for this finding. [18]

Although patients with comorbid disease states (e.g., high cholesterol, heart disease, hypertension) experienced more symptoms such as weight gain, fatigue, and dizziness, no inferences can be made why this phenomenon occurred other than these patients were generally less healthy than the other patients. However, the diagnosis of hypothyroidism may have exacerbated some of these conditions as untreated/undertreated hypothyroidism is associated with these symptoms. No significant differences were found in patients with mood disorders; however, the study was not powered to detect these differences.

There are several potential limitations to this study. Information on patient demographics was not collected (e.g., age, gender, ethnicity) and the ability to conduct a more thorough analysis was reduced. There could potentially be some gender, ethnic, or age variation in response to therapy that was not captured with the symptom assessment scale instrument used in the study. Since patient's literacy levels were not evaluated, it is unknown whether the baseline or health literacy levels in the patient population would have affected their ability to properly complete the survey. The investigators did not capture information on whether or not the respondents were euthyroid prior to the study. If patients were not adequately treated or they were taking medications that may have interfered with levothyroxine absorption, they may still suffer from residual hypothyroid symptoms. However, information related to adherence to thyroid therapy was not attained. There may have been some selection bias as patients who were experiencing residual thyroid symptoms may have been more prone to being included in the study. In addition, the clinical significance of differences in the HSS between intervention and control patients are not known. Additional studies should evaluate the clinical impact of score differences on health-related quality of life.

CONCLUSION

In conclusion, hypothyroidism is a common, yet complex, condition with a wide spectrum of presentation and symptoms. Assessing symptoms, and health status is essential in optimally managing and monitoring the condition. These study results indicate that as many as 15-20% of patients who were receiving a stable dose of levothyroxine, may have residual symptoms

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and form the subset for therapeutic trials using novel therapies. The HSS may be beneficial in helping to identify patients who may continue to have residual thyroid symptoms regardless of thyroid therapy. Additional studies need to be conducted to determine the clinical significance of differences in the HSS.

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Treatment of human subjects: This research was approved by the Samford University Institutional Review Board.
Conflicts of interest: None
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Table 1: Distribution of HSS study participants by Pharmacy

Pharmacies	Contacted	Completed (phone)	Emailed	Declined	Mailed	Non Candidate
Pharmacy 1	117	12	7	0	4	1
Pharmacy 2	91	17	9	4	1	0
Pharmacy 3	122	23	17	5	3	2
Pharmacy 4	72	14	7	7	0	0
Pharmacy 5	99	18	10	5	1	1
Pharmacy 6	170	29	6	12	1	2
Pharmacy 7	43	11	2	4	1	4
Pharmacy 8	125	34	15	0	4	0
Total	839	158	73	37	15	10

Table 2: Differences in symptom score between treatment and control patients

Symptoms	Control (n=273)	Treatment (n=302)	*P*-value
Sum of symptoms	10.07 ± 7.85	13.92 ± 10.91	<0.001
Dry Skin	1.26 ± 1.16	1.75 ± 1.36	<0.001
Fatigue	1.64 ± 1.28	2.05 ± 1.41	<0.001
Weight Gain	1.34 ± 1.31	1.44 ± 1.46	>0.05
Cold Weather Intolerance	1.15 ± 1.36	1.65 ± 1.43	<0.001
Constipation	0.95 ± 1.2	1.22 ± 0.33	<0.05
Muscle Stiffness	1.18 ± 1.3	1.57 ± 1.46	<0.01
Puffiness	0.70 ± 1.06	1.16 ± 0.3	<0.001
Memory Loss	0.72 ± 1.08	1.13 ± 0.29	<0.001
Feeling Blue	0.91 ± 1.17	1.11 ± 0.26	<0.05
Dizziness	0.63 ± 0.95	0.87 ± 0.15	<0.01

Mean ± SD
SD, standard deviation,
Note: Statistical tests of significance performed using the t-test

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Figure 1: Distribution of individual symptom score

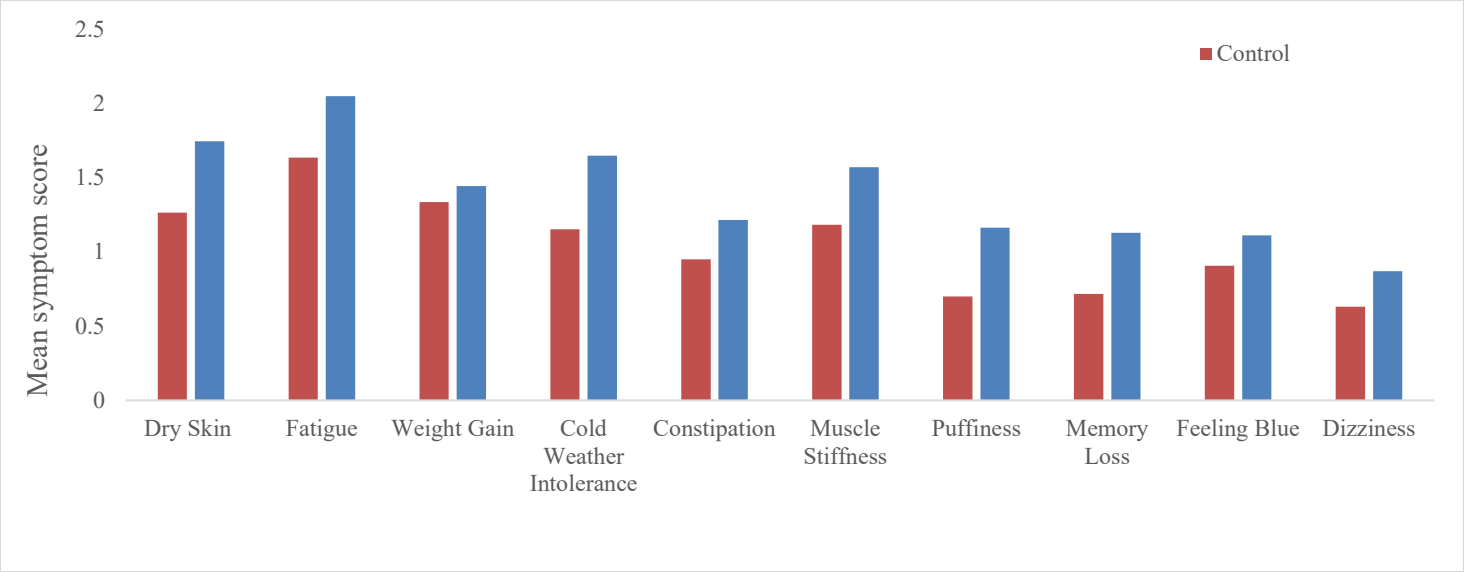

Table 3: Proportion of responding subjects with self-reported medication use and medical comorbidities

	Control (n=269)	Treatment (n=301)	
Condition	n (%)	n (%)	*P*-value
Currently taking other medications	162 (60.2)	266 (80.1)	<0.0001
Heart disease	9 (3.3)	38 (12.6)	<0.0001
High cholesterol	36 (13.2)	95 (31.5)	<0.0001
High blood pressure	71 (26.0)	153 (50.7)	<0.0001
Mood disorder	41 (15.0)	59 (20.0)	>0.05
At least one condition	109 (40)	207 (69)	<0.0001
Not being treated for any of the above	164 (60.1)	95 (31.5)	<0.0001

Tests of statistical significance performed using Chi-square test.

Percentages are row percentages.

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Appendix I: Hypothyroid Symptom Scale Survey

1. Do you agree to the above terms? By clicking Yes, you consent that you are willing to answer the questions in this survey.

A. Yes
B. No

2. Are you currently taking any medications?

A. Yes
B. No

3. Are you currently being treated for any of the following conditions? (Check all that apply).

A. Heart disease
B. High cholesterol
C. High blood pressure
D. Mood disorder
E. None of the above

4. Please indicate the severity to which you have experienced the condition over the past month on a scale of 0 to 4 (absent =0, minimal = 1, mild = 2, moderate =3, and severe =4).

A. Dry skin
B. Fatigue
C. Weight gain
D. Cold weather intolerance
E. Constipation
F. Muscle stiffness
G. Puffiness
H. Memory loss
I. Feeling blue
J. Dizziness

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