Optimal Levothyroxine Replacement Adequately Improves Symptoms of Hypothyroidism; Residual Symptoms Need Further Evaluation for Other than Hypothyroidism Causation

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Abstract

Objectives: Many patients with hypothyroidism complain of persistent residual symptoms, despite optimal treatment, although the similar prevalence is seen in patients with documented absence of thyroid disorder in primary health-care setup. We aimed to investigate symptomatic relief in new cases of primary hypothyroidism and compare with controls with other chronic conditions. Methods: This prospective case–control follow-up study enrolled patients from July 2014 to May 2015 in an endocrine outpatient clinic of a tertiary hospital. Controls were age- and gender-matched ambulatory individuals with well-controlled other chronic diseases and no major comorbidity. Thyroid symptom questionnaire (TSQ) was administered at pretreatment to all the cases and then they were started on levothyroxine (LT). At euthyroidism, TSQ was readministered. For controls, TSQ was administered only once. TSQ was measured on Likert scale 1-4 for lack of energy, dry skin, constipation, aches and pains, cold intolerance, poor memory, depression, weight gain, tiredness after walking, and difficulty in getting up (DGU). P < 0.05 was considered statistically significant. Results: A total of 194 cases (147 females and 47 males) and 259 controls (187 females and 72 males) were analyzed. A significant difference in the symptoms prevalence was seen between controls and pretreatment cases, except for DGU, and between subclinical and overt hypothyroidism. Pretreatment serum thyroid-stimulating hormone in cases correlated significantly with all their pretreatment symptoms score. All symptoms prevalence decreased significantly posttreatment. At euthyroidism, the mean symptoms score in posttreatment cases was similar or lower than the controls. Conclusion: LT effectively improves the symptoms of hypothyroidism in newly diagnosed cases of primary hypothyroidism. The residual symptoms need an alternation explanation other than hypothyroidism.

Keywords: Hypothyroidism, levothyroxine, symptomatic relief

INTRODUCTION

Symptoms of hypothyroidism are subtle and nonspecific.[1] Subclinical and overt primary hypothyroidism usually presents with a typical constellation of clinical symptoms.[2] Tiredness, dry skin (DS), cold sensitivity, fatigue, muscle cramps, and constipation are the most common symptoms in cases of hypothyroidism but lack sensitivity and specificity for making the diagnosis of hypothyroidism.[3] The goal of replacement therapy with levothyroxine 4 (LT4) is amelioration of symptoms and biochemical normalization of serum thyroid-stimulating hormone (TSH).[4] A fair percentage of patients with hypothyroidism report persistence of symptoms despite achieving euthyroidism as seen in large cross-sectional and case-controlled studies.[5,6]

In contrast, a significant percentage of individuals with documented absence of hypothyroidism report typical hypothyroidism symptoms in a primary health-care setting.[7] The reason for residual symptoms in treated cases of hypothyroidism remains elusive and is an area of active research. The persistence of hypothyroidism-like symptoms despite achieving euthyroidism may be due to the tissue-level inadequacy of thyroxine or may be totally unrelated to thyroid...
A study showed that liothyronine in addition to LT reduced the residual psychological symptoms in treated hypothyroidism, but later studies found no difference in the symptoms prevalence between patients receiving combination of liothyronine and thyroxine and those receiving thyroxine alone. In fact, inability of individuals to differentiate between below-normal, mid-normal, and high-normal serum TSH in treated hypothyroid patients for hypothyroidism symptoms, well-being, or quality of life supports the argument that the residual symptoms may be unrelated to hypothyroidism. In most of the case–control studies dealing with this issue, healthy controls were taken from the community. The residual symptoms in optimally treated hypothyroidism cases may be due to psychosomatic component related to a life-long condition requiring life-long treatment or may be due to other coexisting conditions, for example, Vitamin D deficiency, and hence, healthy controls may not be a good option considering the psychosomatic symptoms prevalence in any condition needing life-long treatment.

To address the issue regarding persistent residual symptoms, we conducted this study. We examined the effect of LT in reducing hypothyroidism symptoms in newly detected primary hypothyroidism cases and compared the residuals symptoms with controls at euthyroidism.

**Methods**

**Study design**

The study was designed as a case–control prospective study with longitudinal follow-up. Recruitment of cases commenced in June 2014 and was completed in May 2015. All the consecutive cases presenting with newly diagnosed primary hypothyroidism were assessed for enrollment and were followed up in the Department of Endocrinology of a tertiary care hospital in South India.

**Cases**

Inclusion criteria for cases included newly diagnosed primary or subclinical hypothyroidism, age above 18 years, and being treatment naïve. Primary hypothyroidism was defined as pretreatment serum TSH (pTSH) >10 mIU/L and subclinical hypothyroidism as pTSH 5–10 mIU/L. Subclinical hypothyroidism cases were enrolled if had positive thyroid peroxidase (TPO) antibody. Exclusion criteria included individuals with central hypothyroidism, pregnancy, thyroid malignancy, postradiiodine ablation, or being on LT4, known coronary artery disease or major comorbidity, coprescription of treatment known to affect thyroid hormone metabolism and/or bioavailability, and poor general condition. All patients were enrolled after obtaining written informed consent. Cases were administered a thyroid symptom questionnaire (TSQ) at pretreatment and again after achieving euthyroidism.

**Controls**

Age- and sex-matched controls for each case were taken from the same population, i.e., patients attending outpatient clinic and with confirmed biochemical absence of hypothyroidism. They were taken from the general endocrinology outpatient (OP) department with well-controlled diabetes, thyroid nodule, exogenous obesity, infertility, Vitamin D deficiency, and polycystic ovarian disease; dermatology OP department with nonsystemic skin disorders; and neurology OP department with cervical spondylosis with no neurological deficit and migraine. Otherwise healthy, ambulatory subjects and with no major comorbidity were approached for enrollment. For some cases, age- and gender-matched controls were not available, so ± 1 years’ controls for the same gender were taken. Individuals with chronic but well-controlled conditions were enrolled as controls to adjust for the psychological effect of having chronic diseases. Inclusion criteria included age and sex matching, a latest normal thyroid function report from the Central Laboratory of the Institute.

**Questionnaire**

The TSQ was developed based on common symptoms noted in previous studies. TSQ included questions on: lack of energy (LOE), DS, constipation (C), generalized body aches (AandP), cold intolerance (CI), poor memory (PM), depression (D), weight gain (WG), tiredness after walking (TW), and difficulty in getting up (DGU) from squatting position. DGU was a dummy question (not common in hypothyroidism cases, except with marked serum TSH elevation), put to see the trend of response. The answer of symptoms questionnaire was recorded on Likert scale from 1 to 4. Likert scale was defined as follows: 1 – symptoms absent, 2 – rarely present, 3 – present, and 4 – severely present. A single research assistant administered the questionnaire to all the cases and controls.

**Study protocol**

After administering the TSQ, all cases were started on LT treatment. The LT4 dose was adjusted every 6–10 weeks to achieve optimal physiological hormonal replacement and target range serum TSH (0.4–4.5 mIU/L), i.e., euthyroidism. Patients were explained and reemphasized at every visit to take LT4 in morning empty stomach, maintain a gap of at least 1 h food and beverages, and maintain gap of at least 4 h between LT4 and coprescription with calcium or iron supplements or proton-pump inhibitor. Each patient received LT4 as per the routine protocol of treatment. Once these patients achieved reference range TSH levels (0.4–4.5 mIU/L), the TSQ was readministered by the research assistant. The anthropometric and demographic data were collected for all. Height was measured to the nearest 0.1 cm using a stadiometer, with a patient standing straight with head held in Frankfurt horizontal plane, and coefficient of variance (CV) of measurement was <1%. Weight was checked without shoes and with light clothes measured to the nearest 0.1 kg using an electronic scale, and CV was 1.35%. The same research assistant took all the measurements. Individuals not achieving euthyroidism during the study period were dropped from the study. As per protocol, only 100% medication complaint patients at euthyroidism were considered to have completed the study, i.e., achieved euthyroidism.
Pilot study
Initially, a pilot study was done with 38 cases (21 patients completed the study, i.e., achieved euthyroidism) to find the mean and standard deviation (SD) of symptoms. A total of 26 age- and sex-matched controls with other chronic disease, ambulatory, no major comorbidity, and well-controlled disease status were enrolled. The data obtained by pilot study were used to find the sample size for assessing the change in mean of symptoms on Likert scale. 1,2,3,4 To assess the response process validity, interpretation of questionnaire, and response by participants, the questionnaire was administered in the pilot study cases.

Hormonal measurement
For all the cases and controls, biochemical test was done in the Central Laboratory of the Institute. Serum TSH analysis was done by chemiluminescence immunoassay method (Roche Cobas e411) with functional sensitivity, 0.005 mIU/L; normal range, 0.4–4.5 mIU/L. Lyophilized quality-control materials (Bio-Rad) with mean values of three levels of controls being 0.46, 5.52, and 34.2 mIU/L were used. The inter- and intra-assay variability was 2.9 and 3. TPO antibody was measured by immunoassay (Calbiotech, USA). TPO index was calculated by dividing the levels of TPO antibody by laboratory upper normal limit.

Ethics
The protocol was approved by the institutional ethical review board, and the study was conducted in accordance with the Declaration of Helsinki. Patients were enrolled after obtaining written informed consent.

Statistical analyses
A sample size of 201 was calculated, considering 30% drop out expected for follow-up study the total sample size calculated was 261. Descriptive statistics of demographic and clinical data were calculated. Continuous data have been expressed as mean ± SD, and Likert scale data were expressed as percentage. The symptoms score of 3 and 4 is clubbed for defining the symptoms prevalence. Cronbach’s alpha assessed internal consistency and reliability. Pearson’s method and Spearman’s method were used for correlation coefficient as required. All correlation analysis was two-tailed. Comparison of percentage between groups was done by Pearson’s Chi-square test. For comparisons of means between two related groups, we used Student’s t-test. P < 0.05 was considered statistically significant.

Effect size was calculated as Cohen’s d and is defined as small for 0.2, medium 0.5, and large 0.8. 15,16,17 Only completed cases were used for analysis. Binary logistic regression by forward logistics was used to calculate odds ratio. All data were analyzed by SPSS version 16 (SPSS, Chicago, IL, USA).

Results
A total of 337 cases and 259 controls were enrolled, and 194 cases completed the study, i.e., achieved euthyroidism during the study period. The flowchart of enrollment is shown in Figure 1. The baseline characteristics of the completed cases, dropped cases, and controls are presented in Table 1. No significant difference in the baseline characteristics or symptoms’ prevalence was seen between completed and dropped cases. The reasons given for withdrawal during follow-up of cases were inability to attend study visit. None of the cases reported unacceptable symptoms. All the completed cases had 100% compliance to LT as per protocol. The overall prevalence of the symptoms in pretreatment group, posttreatment group, and control for TSQ-LOE was 57.3%, 2.5%, and 18.2%; TSQ-DS 14.3%, 1%, and 3.1%; TSQ-C 28.4, 3.5%, and 9.3%; TSQ-AandP 61.9%, 10.2%, and 38.2%, TSQ-CI 18.8%, 1%, and 6.6%; TSQ-PM 23.8%, 4.6%, and 14%; TSQ-D 23.3%, 2%, and 3.9%; TSQ-WG 28.9%, 5.1%, and 15.1%; TSQ-TW 39%, 2.5%, and 9.7%; and TSQ-DGU 24%, 6.1%, and 21.3, respectively, and is depicted in Figure 2. Prevalence of symptoms score in male and female is summarized separately for the pretreatment group, posttreatment group, and control in Table 2. Overall prevalence of symptoms in posttreatment cases was 27%, while in controls, 69% reported the presence of one or other symptoms. The effect size of reduction in symptoms score between pretreatment and posttreatment phase is shown separately in both genders in Table 2.

Weight decreased significantly in cases from pretreatment (mean weight 62.95 ± 13.7 kg) to posttreatment state (mean weight 62.54 ± 13.5 kg), P < 0.05. Among the completed cases, 56 (51 women, 5 men) had subclinical hypothyroidism and 138 (96 women, 42 men) cases had overt hypothyroidism. The prevalence of symptoms in subclinical and overt hypothyroidism cases for TSQ-LOE was 32.4% and 66.0%, TSQ-DS 4.1% and 17.6%, TSQ-C 10.2% and 34.0%, TSQ-AandP 48.0% and 67.0%, TSQ-CI 14.6% and 20.2%, TSQ-PM 12.5% and 27.9%, TSQ-D 8.3% and 28.6%, TSQ-WG 16.7% and 33.3%, TSQ-TW 18.9% and 45.5%, and TSQ-DGU 8.3% and 29.3%, respectively, and was significantly different for all the symptoms. Compared to controls, the mean symptoms score was significantly higher in subclinical hypothyroidism for TSQ-LOE, TSQ-DS, TSQ-PM, TSQ-D, and TSQ-TW, while TSQ-DGU was higher in controls.

Figure 1: The enrollment flowchart of cases and control
For assessing reliability and internal construct validity, Cronbach’s alpha estimation for the symptoms was done. On entering all the items in the analysis, the alpha value was 0.754. On deleting WG, DS, and constipation, the alpha value increased to 0.790. No further increase in alpha value was seen with deletion of another item. For validation of symptoms for hypothyroidism, correlation of symptoms with serum TSH was evaluated. All the hypothyroidism symptoms correlated significantly with pTSH; TSQ-LOE $r = 0.41$, $P < 0.001$; TSQ-D $r = 0.33$, $P < 0.001$; TSQ-C $r = 0.25$, $P < 0.001$; TSQ-Aa&D $r = 0.31$, $P < 0.001$; TSQ-CI, $r = 0.28$, $P < 0.001$; TSQ-PM $r = 0.20$, $P < 0.01$; TSQ-D $r = 0.32$, $P < 0.001$; TSQ-WG $r = 0.20$, $P < 0.01$; TSQ-TW $r = 0.32$, $P < 0.001$; and TSQ-DGU $r = 0.31$, $P < 0.001$. TPO index correlated significantly with TSQ-WG, and a trend of significance was seen for TSQ-DGU. The correlation between TSQ-WG remained significant even after adjusting for pTSH. The trend for the correlation of TSQ-DGU disappeared after adjusting for weight. The good correlation of all the hypothyroidism symptoms with pTSH (pretreatment) provides validity to the questionnaire, as serum TSH is the most sensitive marker of thyroid hormone level in circulation in primary hypothyroidism. In the posttreatment phase, there was no significant difference in the symptoms between the cases with TSH <2.5 mIU/L versus TSH ≥2.5 mIU/L. The mean symptoms score in posttreatment phase of cases between cases with TSH <2.5 mIU/L versus TSH ≥2.5 mIU/L is shown in Table 3. No correlation was seen between the posttreatment serum TSH and posttreatment symptoms score. No significant correlation was seen in controls between baseline serum TSH and hypothyroid symptoms, except for a significant negative correlation between tiredness and serum TSH ($r = -0.12$, $P = 0.04$). The likelihood of hypothyroidism as per the symptoms score in cases versus controls was assessed by logistic regression. The odds ratio for likelihood of hypothyroidism diagnosis based on symptoms in multivariate model is shown in Table 4. TSQ-CI and TSQ-C did not enter in the multivariate logistic regression model.

### Table 1: Baseline characteristics of the cases of primary hypothyroidism completing the study, dropped cases, and controls are expressed as mean±standard deviation

| Variables         | Completed cases (n = 194) | Dropped cases (n = 143) | All controls (n = 259) |
|-------------------|----------------------------|-------------------------|------------------------|
| Age, years        | 37.1±12.9                  | 29.8±13.2               | 39.4±13.8              |
| Weight, kg        | 62.9±13.7                  | 64.2±14.6               | 64.5±15.1              |
| Height, cm        | 156.5±7.6                  | 157.6±9.1               | 157.2±9.3              |
| BMI, kg/m²        | 25.8±5.1                   | 25.8±5.0                | 27.9±5.5               |
| TPO ratio         | 3.9±4.7                    | 5.0±5.4                 | Not done               |
| Serum TSH mIU/L   | 52.7±49.9                  | 38.6±44.0               | 2.7±1.3*               |

*P<0.05 was considered significant; *Significant seen between cases and control. BMI: Body mass index, TPO: Thyroid peroxidase antibody, TSH: Thyroid-stimulating hormone

### Table 2: The percentage of subjects with symptoms (score 3 and 4 clubbed together) in pretreatment * and posttreatment cases and controls in both the genders separately

| Symptoms        | Femalea,b | Malea,b | Femalec | Malec | Femaled,β | Maled,β | Female* | Male* |
|-----------------|-----------|---------|---------|-------|-----------|---------|---------|-------|
| TSQ-LOE         | 63.4 (2.8±1.2) | 43.7 (2.3±1.2) | 1.1 (1.2±0.5) | 2.2 (1.3±0.6) | 21.0 (1.8±0.8) | 7.0 (1.4±0.7) | 2.3† | 1.6† |
| TSQ-DS          | 12.4 (1.4±0.8) | 20.9 (1.5±0.9) | 1.6 (1.0±0.3) | 0 (1.0±0.0) | 2.7 (1.1±0.3) | 8.4 (1.1±0.4) | 0.8† | 1.0† |
| TSQ-C           | 27.6 (1.8±1.1) | 31.3 (1.9±1.2) | 2.3 (1.2±0.5) | 1.1 (1.1±0.4) | 9.7 (1.3±0.7) | 7.5 (1.6±1.9) | 0.9† | 1.4† |
| TSQ-Aa&D        | 65.8 (2.8±1.2) | 54.2 (2.5±1.2) | 6.7 (1.6±0.8) | 2.2 (1.3±0.7) | 43.9 (2.2±1.1) | 22.5 (1.7±0.9) | 1.6† | 2.1† |
| TSQ-CI          | 21.2 (1.6±0.9) | 12.5 (1.4±0.8) | 0.8 (1.0±0.3) | 0 (1.0±0.2) | 7.4 (1.2±0.5) | 4.2 (1.2±0.5) | 0.9† | 0.7  |
| TSQ-PM          | 27.6 (1.8±0.9) | 14.6 (1.5±0.8) | 1.9 (1.2±0.5) | 4.3 (1.3±0.6) | 4.3 (1.2±0.5) | 2.8 (1.2±0.4) | 1.1† | 0.7  |
| TSQ-D           | 22.1 (1.6±0.9) | 29.2 (1.7±1.0) | 0.8 (1.1±0.4) | 2.2 (1.2±0.6) | 4.8 (1.1±0.5) | 1.5 (1.0±0.3) | 1.0† | 1.1† |
| TSQ-WG          | 27.4 (1.7±1.0) | 33.4 (1.8±1.0) | 3.4 (1.2±0.5) | 1.1 (1.0±0.3) | 17.1 (1.4±0.8) | 9.8 (1.3±0.8) | 0.9† | 1.4† |
| TSQ-TW          | 42.5 (2.0±1.0) | 29.1 (1.8±1.0) | 2.9 (1.0±0.2) | 0 (1.0±0.2) | 11.2 (1.4±0.7) | 5.6 (1.2±0.5) | 1.5† | 1.3† |
| TSQ-DGU         | 26.7 (1.7±0.9) | 16.7 (1.5±0.9) | 3.4 (1.2±0.5) | 3.2 (1.2±0.5) | 24.8 (1.7±0.9) | 12.3 (1.4±0.8) | 1.1† | 0.8† |

All symptoms are represented as percentage (mean±SD). All the values are in percentage (mean±SD). TSQ: Thyroid symptom questionnaire, LOE: Lack of energy, DS: Dry skin, C: Constipation, Aa&D: Aches and pain, CI: Cold intolerance, PM: Poor memory, D: Depression, WG: Weight gain, TW: Tiredness while walking, DGU: Difficulty in getting up.

**DISCUSSION**

There is a growing debate on the optimal treatment of hypothyroid patients for adequate symptomatic relief. Most of the information on symptomatic relief with optimal LT treatment in hypothyroidism is from cross-sectional studies.
with long-standing hypothyroidism or from case–control studies where controls were taken from the healthy population.[5–7] Hypothyroidism is a chronic disease, and the need for life-long therapy by itself may affect the psychological well-being. No study has addressed the component of psychosomatic symptoms in a chronic condition such as hypothyroidism. To address this issue, case–control studies are needed with controls recruited from subjects with stable chronic conditions which can have similar psychosomatic symptoms. Longitudinal follow-up study in newly diagnosed primary hypothyroidism for symptomatic relief on replacement with levothyroxine is lacking. This study addressed the issues of symptomatic relief on optimal LT therapy from pretreatment to posttreatment phase in newly diagnosed primary hypothyroidism. This study showed a very good response to treatment for all the symptoms evaluated.

Our study showed a very good symptomatic relief with treatment in both genders. The effect size for symptomatic relief was good for all the symptoms. The symptoms at euthyroidism in these cases were lower or similar to controls. A previous study showed that symptoms of hypothyroidism and ill health persist despite optimal LT4 treatment in >13% population.[7] In our study, we found that these symptoms were not more than controls. In fact, the prevalence of few of the symptoms was significantly less in posttreatment group as compared to controls. Controversy exists for the reasons behind the inadequate symptomatic relief even at biochemical euthyroidism on LT4. Studies in thyroidectomized rats have shown that replacement therapy with LT alone is not enough to achieve euthyroidism in all tissues and adding LT3 with LT4 helps in achieving all tissue euthyroidism and improves mood and neurocognition.[8,9] However, later trials investigating the effect of combined treatment with LT4 and LT3 versus LT4 only did not improve thyroid symptoms, quality of life, and psychological status.[10,11]

In the present study, LOE, AandP, TW, and WG were common symptoms in cases before treatment. All the symptoms were more prevalent in pretreatment cases compared to controls. Similar findings were seen in other studies.[14,15] The Colorado study found tiredness, DS, and cold sensitive as the most common hypothyroid symptoms.[15] In the study by Carle et al.,[16] tiredness (81%), DS (63%), generalized pain (47%), and constipation (39%) were the most common symptoms in cases, while in age- and sex-matched controls, the most common symptoms were tiredness (41%), DS (29%), generalized pain (39%), and constipation (17%).[15] As expected, symptoms scores were significantly different between subclinical hypothyroidism and overt hypothyroidism with the higher symptoms score in overt hypothyroidism compared to subclinical case. This finding of our study is similar to the Colorado study.[15] The prevalence of all the ten symptoms decreased significantly in cases from pretreatment to posttreatment state in the present study, and symptomatic relief was better than other reported study. The poor response to treatment in Carle’s study may be explained by the fact that 30% cases did not achieve target range serum TSH in the study,[16] whereas the good response to treatment in the current study can be explained by the fact that all the cases achieved euthyroidism.

No significant difference in symptoms score was seen between cases in posttreatment phase with TSH <2.5 mIU/L and TSH ≥2.5 mIU/L. The study by Walsh et al. supports the findings of this study as patients with hypothyroidism on LT treatment could not differentiate in residual symptoms below-normal range serum TSH (<0.3 mIU/L), low-normal reference range serum TSH (0.3–1.99 mIU/L), and high-normal serum TSH (2.0–4.8 mIU/L) brought by slight changes in small LT4 dosage (20%).[11] Hence, our study suggests a very good response to LT treatment for all the evaluated symptoms in men and women. The higher the pTSH, higher is the symptoms prevalence; however, on achieving euthyroidism, all the

### Table 3: The mean thyroid symptoms score in cases group based on posttreatment thyroid-stimulating hormone <2.5 mIU/L and thyroid-stimulating hormone ≥2.5 mIU/L

| Symptoms | TSH <2.5 mIU/L | TSH ≥2.5 mIU/L | P  |
|----------|----------------|----------------|----|
| TSQ-LOE  | 1.2±0.5        | 1.3±0.5        | 0.6|
| TSQ-DS   | 1.0±0.2        | 1.0±0.2        | 0.8|
| TSQ-C    | 1.2±0.4        | 1.2±0.5        | 0.9|
| TSQ-AandP| 1.5±0.8        | 1.6±0.8        | 0.6|
| TSQ-CI   | 1.1±0.3        | 1.0±0.3        | 0.03*|
| TSQ-PM   | 1.2±0.5        | 1.2±0.5        | 0.5|
| TSQ-D    | 1.2±0.4        | 1.1±0.5        | 0.2|
| TSQ-WG   | 1.1±0.5        | 1.2±0.5        | 0.3|
| TSQ-TW   | 1.2±0.5        | 1.3±0.5        | 0.05|
| TSQ-DGU  | 1.1±0.4        | 1.3±0.6        | 0.08|

Symptom score is represented as mean±SD. *P<0.05 was considered significant. TSQ: Thyroid symptom questionnaire, LOE: Lack of energy, DS: Dry skin, CI: Cold intolerance, PM: Poor memory, D: Depression, WG: Weight gain, TW: Tiredness while walking, DGU: Difficulty in getting up, SD: Standard deviation, TSH: Thyroid-stimulating hormone.

### Table 4: Odds ratio for diagnosing hypothyroidism based on symptoms score at pretreatment cases versus controls

| Symptoms | OR  | P    | 95% CI |
|----------|-----|------|--------|
| TSQ-LOE  | 1.7 | 0.001| 1.3–2.2|
| TSQ-DS   | 1.6 | 0.05 | 1.0–2.5|
| TSQ-AandP| 1.4 | 0.006| 1.1–1.8|
| TSQ-PM   | 1.7 | 0.009| 1.1–2.5|
| TSQ-D    | 1.9 | 0.004| 1.2–2.9|
| TSQ-WG   | 1.4 | 0.01 | 1.1–1.9|
| TSQ-TW   | 1.4 | 0.05 | 1.0–1.9|
| TSQ-DGU  | 0.5 | 0.001| 0.3–0.6|

P<0.05 was considered significant. TSQ: Thyroid symptom questionnaire, LOE: Lack of energy, DS: Dry skin, CI: Constipation, AandP: Aches and pain, CI: Cold intolerance, PM: Poor memory, D: Depression, WG: Weight gain, TW: Tiredness while walking, DGU: Difficulty in getting up, CI: Confidence interval, OR: Odds ratio.

In our study, we found that these symptoms were not more than controls. In fact, the prevalence of few of the symptoms was significantly less in posttreatment group as compared to controls. Controversy exists for the reasons behind the inadequate symptomatic relief even at biochemical euthyroidism on LT4. Studies in thyroidectomized rats have shown that replacement therapy with LT alone is not enough to achieve euthyroidism in all tissues and adding LT3 with LT4 helps in achieving all tissue euthyroidism and improves mood and neurocognition.[8,9] However, later trials investigating the effect of combined treatment with LT4 and LT3 versus LT4 only did not improve thyroid symptoms, quality of life, and psychological status.[10,11]
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symptoms decrease effectively. Some patients complained of residual symptoms typical of hypothyroidism, even at biochemical euthyroidism. However, these symptoms typical of hypothyroidism such as DS, constipation, and WG were also seen in controls in whom euthyroidism was confirmed. Most of the residual symptoms prevalence in euthyroid cases was either less or similar to the controls. Therefore, findings of this study suggest looking for an alternate explanation for the residual symptoms.

The main strength of this study is the enrollment and follow-up of newly diagnosed hypothyroidism cases, large sample size, longitudinal study design, selection of controls with chronic disease with no major comorbidity, inclusion of common hypothyroidism symptoms, latest euthyroid status based on biochemistry, confirmed biochemistry from a single laboratory in all cases, and use of euthyroid case only for final analysis.

**Conclusion**

LT treatment in primary hypothyroidism reduces symptoms significantly. The residual symptoms at euthyroidism were either similar or significantly less than age- and sex-matched controls.

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**Conflicts of interest**
There are no conflicts of interest.

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