Effect of Levothyroxine Replacement on Cognitive Function Impairment in a Sample of Egyptian Population with Subclinical Hypothyroidism

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Keywords
Cognitive impairment · Subclinical hypothyroidism · Egyptian population · Levothyroxine · Addenbrooke’s questionnaire

Abstract
Introduction: Subclinical hypothyroidism (SHT) is characterized by a normal range of free thyroxin concentrations together with increased serum TSH levels. SHT is defined as an abnormal range of thyroid-stimulating hormone (TSH) concentration above the upper limit of the reference range in the face of normal free FT4 and FT3 levels. The effect of SHT on cognitive function has been investigated in several preclinical studies, and a growing body of evidence has suggested a relevant link between thyroid hormones and the central nervous system. Objectives: This study aimed to investigate the effect of levothyroxine replacement on cognitive impairment in a sample of Egyptian patients with SHT. Methods: A prospective cohort study conducted on 30 patients with cognitive impairment and SHT attending an endocrine outpatient clinic at the Ain Shams University Hospital to study the effect of levothyroxine supplementation on cognitive impairment in patients with SHT. The study was conducted on 30 patients. All participants were subjected to a full history taking; thorough clinical examination; laboratory investigations including thyroid profile (FT3, FT4, TSH), anti-thyroid peroxidase antibodies, anti-thyroglobulin antibodies, and lipid profile; imaging tests as neck ultrasound, echocardiography, and carotid duplex; and finally Addenbrooke’s questionnaire used to diagnose mild cognitive impairment. Results: A highly statistically significant difference was found before, 3 months and 6 months after treatment with levothyroxine regarding all clinical data, TSH, LDL, T. cholesterol, FT3, FT4 and HDL, carotid intima-media thickness, and Addenbrooke’s questionnaire. Our study showed a statistically significant inverse correlation between TSH level and mild cognitive impairment before and after treatment with levothyroxine at 3 and 6 months intervals as when TSH increased, results of Addenbrooke’s questionnaire decreased and, so, cognitive impairment increased, while when TSH decreased in response to thyroxine replacement, cognitive impairment improved as detected by an increase in the patient’s score. Conclusion: SHT has a great effect on cognitive impairment, as normalization in TSH level results in improvement in cognitive function. Also, there was a significant reduction in carotid intima-media thickness, which may contribute to improvement of cognitive function in addition to a great improvement in lipid profile, which in turn positively affects cardiac and cognitive function.

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Introduction

Thyroid hormone regulates myelination, growth, and puberty in the neural system, as well as metabolism and organ functions [1]. Hypothyroidism in early life, known as congenital hypothyroidism, has been documented to produce problems such as mental retardation and delayed myelination [2, 3].

Mild thyroid failure, also known as subclinical hypothyroidism (SHT), is defined as thyroid-stimulating hormone (TSH) levels over the upper limit of the reference range in the presence of normal FT4 and FT3 levels [4, 5]. SHT is linked to several diseases, the most common of which being chronic autoimmune thyroiditis (Hashimoto’s thyroiditis) [4].

The ability to process thoughts is referred to as cognitive function. As hypothyroidism affects cognitive skills and mood, cognition relates to memory, speech, reading comprehension, and learning something new [6].

Several research studies have investigated the impact of SHT on cognitive function, and evidence has shown a close link between thyroid hormones and the central nervous system [7]. However, the true direct link between SHT and cognitive impairment or dementia risk has yet to be fully elucidated [7].

When the TSH level exceeds 10.0 mIU/L, levothyroxine medication is suggested. However, the available information on the dangers and advantages of treatment for people with TSH 10.0 mIU/L (mild-SCH) is still debated, and there is no consensus on the clinical significance of side effects or the benefits of thyroxine medication in individuals with TSH 10.0 mIU/L. One of the explanations could be that SCH patients with varying levels of TSH and thyroid dysfunction were included in all of the research on the negative consequences [8].

Aim of the Work

The aim of this work was to study the effect of levothyroxine therapy on cognitive impairment in a sample of Egyptian patients with SHT.

Patients and Methods

This was a prospective cohort study conducted on 30 patients with cognitive impairment and SHT attending endocrine outpatient clinic at the Ain Shams University Hospital during period from August 2020 to February 2021 to study the effect of levothyroxine treatment on cognitive impairment in patients with SHT.

Inclusion Criteria

Both sexes were included. Age ranges from 50 to 60 years old, as older people (>75 years) are more likely to have more precipitating factors for dementia as atherosclerosis and vascular diseases that confound our investigation regarding effect of isolated SHT on cognitive impairment. Also, lack of age-related TSH reference ranges, and there can be consequent misdiagnosis of SHT in elderly. SHT patients with TSH >10 with cognitive impairment.

Exclusion Criteria

Any patient with overt hypothyroidism, ischaemic heart disease, any arrhythmias, or heart failure. Other diseases affecting cognitive function like neurological disorders as strokes and multi-infarcts dementia, psychological disorders, chronic kidney disease, chronic liver disease. Drugs affecting cognitive function, as history of drug abuse, alcohol dependence, antidepressants, antipsychotics, sedatives.

All participants of this study were subjected to the following:

History-taking including age, sex, duration of the disease, symptoms. Also, thorough clinical examination emphasizing on pulse, blood pressure, weight, height, BMI, neck examination. Laboratory investigations including thyroid profile (free T3, free T4, TSH). SHT is diagnosed by high titre of TSH; normal FT3 and FT4 level reference range: TSH (0.27–4.20) µIU/mL, FT3 (2.00–4.40) pg/mL, FT4 (0.93–1.70) ng/dL; anti-thyroid peroxidase; anti-thyroglobulin antibodies; and lipid profile. Imaging including neck ultrasound, echocardiography, and carotid duplex to assess carotid intima-media thickness.

The Addenbrooke’s Cognitive Examination III (2012) is a cognitive tool that evaluates a variety of cognitive abilities. Its five subcategories (attention and orientation, memory, verbal fluency, language, and visual-spatial abilities), with a maximum score of 100, are typically impaired in dementias. The normal Addenbrooke’s Cognitive Examination III score is ≥96, with one point added if the subject has less than 12 years of formal education.

The patient will receive levothyroxine 50 μg per day in the early morning before meals then follow-up after 2 weeks by history-taking for palpitation and clinical assessment (pulse and blood pressure) and follow-up every 6–8 weeks to assess side effects of the drug. Then after 3 and 6 months, follow-up of thyroid profile, lipid profile, carotid intima-media thickness, and Addenbrooke’s questionnaire will be performed. In case of any adverse events as arrhythmia, levothyroxine will be stopped.

Statistical Analysis

Statistical presentation and analysis of the present study were conducted using the mean, standard deviation (as the variables are normally distributed), paired t-test, and Pearson’s correlation coefficient by SPSS V20. Paired t-test was used to determine whether the mean difference between two sets of observations is zero (when differences are normally distributed).

Pearson’s Correlation Coefficient (r)

Pearson’s correlation coefficient was used for detection of correlation between two quantitative variables in one group. p value >0.05 nonsignificant. p value ≤0.05 significant. p value <0.01 highly significant.
Results

This was a prospective cohort study conducted on 30 patients with cognitive impairment and SHT attending endocrine outpatient clinic at the Ain Shams University Hospital to study the effect of levothyroxine on cognitive impairment in patients with SHT. Results are expressed in Tables 1–4.

Descriptive analysis for all studied patients regarding demographic and laboratory data before treatment showed that age group ranges from 50 to 60 years with mean (54.733 ± 2.912) years, with mean weight 87.967 ± 8.036 kg, while mean height (165.467 ± 3.401) cm. For BMI, it had a mean of (32.110 ± 3.228) kg/m². Also, showed that age group ranges from 50 to 60 years with mean (54.733 ± 2.912) years, with mean weight 87.967 ± 8.036 kg, while mean height (165.467 ± 3.401) cm. For BMI, it had a mean of (32.110 ± 3.228) kg/m². Also, results showed that mean SBP before treatment is (133.667 ± 9.643) mm Hg, while mean of DBP is (85.500 ± 7.234) mm Hg with a mean pulse (67.867 ± 5.823) b/m. TSH had a mean of (14.927 ± 2.585) µIU/mL, while mean FT4 was (1.345 ± 0.257) ng/dL with mean FT3 (3.068 ± 0.654) pg/mL. Anti-thyroid peroxidase antibody’s mean level was found to be (79.267 ± 50.033) IU/mL, while anti-thyroglobulin antibody’s mean level was (197.400 ± 94.209) IU/mL. HDL level before treatment had a mean of (43.800 ± 8.965) mg/dL, while mean LDL was (150.433 ± 21.633) mg/dL with mean triglycerides (127.967 ± 15.048) mg/dL, with T. cholesterol mean level (231.300 ± 21.963) mg/dL. Also, showed that there is a statistically significant difference was found regarding BMI with treatment with p value (<0.001) for both, with mean (90.000 ± 1.145) (Tables 1, 2).

Comparison between results before, 3 months and 6 months after treatment regarding anthropometric measures, clinical data, and laboratory data. This table showed that a statistically significant difference was found regarding weight before, 3 months and 6 months after levothyroxine treatment which shows reduction in weight with p value (<0.001) for both, with mean (86.967 ± 7.77, 84.533 ± 7.459) kg, respectively.

Also, showed a significant difference regarding BMI before, 3 months and 6 months after levothyroxine treatment which shows reduction in BMI with p value (<0.001) for both, with mean (31.750 ± 3.109, 30.860 ± 3.036), respectively. This table showed a significant increase in pulse before, 3 months and 6 months after levothyroxine treatment with p value (<0.001) for both, with mean (76,000 ± 5.458, 83.067 ± 4.193) b/m, respectively.

This table also showed that there is a statistically significant reduction in SBP before, 3 months and 6 months after levothyroxine treatment with p value (<0.001) for both, with mean (126.667 ± 7.581, 121.333 ± 5.713) mm Hg, respectively. Also, showed that there is a statistically significant reduction in DBP before, 3 months and 6 months after levothyroxine treatment with p value (<0.001) for both, with mean (81.833 ± 5.943, 78.333 ± 5.142) mm Hg, respectively. Also, there was a significant difference in level of TSH before, 3 months and 6 months after levothyroxine treatment which showed reduction of TSH value with treatment with p value (<0.001) for both, with mean (9.915 ± 2.473, 5.033 ± 2.009) µIU/mL, respectively.

A significant difference between level of FT4 before, 3 months and 6 months after levothyroxine treatment was found as it increased with p value (0.047 and 0.030), respectively, with mean (1.515 ± 0.298, 1.599 ± 0.467) ng/dL, respectively. Also, there was a statistically significance difference in level of FT3 before, 3 months and 6 months after levothyroxine treatment which increased with p value (0.024 and 0.044), respectively, with mean (3.399 ± 0.531, 3.433 ± 0.580) pg/mL, respectively.

This table showed a statistically significant difference between HDL level before, 3 months and 6 months after levothyroxine treatment which showed improvement with p value (<0.004 and <0.001), respectively, with mean (47.033 ± 7.402, 49.733 ± 10.654) mg/dL, respectively.

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Table 1. Shows descriptive analysis for all studied patients regarding demographic and laboratory data before treatment

| Descriptive statistics | range | mean ± SD |
|------------------------|-------|-----------|
| Age, years             | 50–60 | 54.733±2.912 |
| Weight, kg             | 73–105 | 87.967±8.036 |
| Height, cm             | 159–175 | 165.467±3.401 |
| BMI, kg/m²             | 25.8–38.5 | 32.110±3.228 |
| SBP, mm Hg             | 110–150 | 133.667±6.463 |
| DBP, mm Hg             | 70–100 | 85.500±7.234 |
| Pulse, beat/min        | 60–80 | 67.867±5.823 |
| TSH, µIU/mL            | 10.69–19.2 | 14.927±2.585 |
| Free T4, ng/dL         | 0.92–1.75 | 1.345±0.257 |
| Free T3, pg/mL         | 2.1–4.13 | 3.068±0.654 |
| HDL, mg/dL             | 32–64 | 43.800±8.965 |
| LDL, mg/dL             | 99–151 | 127.967±15.048 |
| Triglycerides, mg/dL   | 191–268 | 231.300±21.963 |
| Total cholesterol, mg/dL | 0.63–1.21 | 0.993±0.168 |
| Carotid intima-media thickness, mm | 89–93 | 90.000±1.145 |
| Addenbrooke’s questionnaire | 10–178 | 79.267±50.033 |
| Anti-TPO, IU/mL        | 29–390 | 179.400±94.209 |
| Anti-thyroglobulin, IU/mL | 29–390 | 179.400±94.209 |

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TPO, thyroid peroxidase.
### Table 2. Comparison between results before, 3 months and 6 months after treatment regarding anthropometric measures, clinical data, and laboratory data

| Time Range | Range | Mean ± SD | COMP. Differences | Paired test |
|------------|-------|-----------|-------------------|-------------|
| **Weight, kg** | | | | |
| Pre | 73–105 | 87.967±8.036 | P-P3 months | 1.000 0.695 7.883 <0.001* |
| Post 3 months | 73–103 | 86.967±7.770 | P-P6 months | 3.433 2.128 8.836 <0.001* |
| Post 6 months | 73–98 | 84.533±7.459 | P3-P6 months | 2.433 1.633 8.160 <0.001* |
| **BMI, kg/m²** | | | | |
| Pre | 25.8–38.5 | 32.110±3.228 | P-P3 months | 0.360 0.267 7.377 <0.001* |
| Post 3 months | 25.8–37.8 | 31.750±3.109 | P-P6 months | 1.250 0.764 8.965 <0.001* |
| Post 6 months | 25.8–35.9 | 30.860±3.036 | P3-P6 months | 0.890 0.586 8.323 <0.001* |
| **Pulse** | | | | |
| Pre | 60–80 | 67.867±5.823 | P-P3 months | −8.133 4.607 −9.670 <0.001* |
| Post 3 months | 66–88 | 76.000±5.458 | P-P6 months | −15.200 4.567 −18.230 <0.001* |
| Post 6 months | 76–90 | 83.067±4.193 | P3-P6 months | −7.067 2.815 −13.748 <0.001* |
| **SBP** | | | | |
| Pre | 110–150 | 133.667±9.643 | P-P3 months | 7.000 5.350 7.167 <0.001* |
| Post 3 months | 110–140 | 126.667±7.581 | P-P6 months | 12.333 8.172 8.266 <0.001* |
| Post 6 months | 110–130 | 121.333±5.713 | P3-P6 months | 5.333 5.074 5.757 <0.001* |
| **Free T3** | | | | |
| Pre | 2.1–4.13 | 3.068±0.654 | P-P3 months | −0.331 0.761 −2.380 0.024* |
| Post 3 months | 2.15–4.22 | 3.399±5.321 | P-P6 months | −0.365 0.947 −2.109 0.044* |
| Post 6 months | 2.25–4.27 | 3.433±0.580 | P3-P6 months | −0.034 0.857 −0.217 0.830 |
| **Free T4** | | | | |
| Pre | 0.92–1.75 | 1.34±0.257 | P-P3 months | −0.171 0.449 −2.080 0.047* |
| Post 3 months | 0.92–2.75 | 1.515±0.298 | P-P6 months | −0.255 0.610 −2.286 0.030* |
| Post 6 months | 1.1–3.82 | 1.599±0.467 | P3-P6 months | −0.084 0.340 −1.354 0.186 |
| **TSH** | | | | |
| Pre | 10.69–19.2 | 14.92±2.585 | P-P3 months | 5.013 2.605 10.539 <0.001* |
| Post 3 months | 1.55–13.25 | 9.91±2.473 | P-P6 months | 9.894 2.860 18.951 <0.001* |
| Post 6 months | 1.23–8.46 | 5.03±2.009 | P3-P6 months | 4.882 1.894 14.116 <0.001* |
| **HDL** | | | | |
| Pre | 32–64 | 43.800±8.965 | P-P3 months | −3.233 5.679 −3.118 0.004* |
| Post 3 months | 35–65 | 47.03±7.402 | P-P6 months | −5.933 8.650 −3.757 0.001* |
| Post 6 months | 35–70 | 49.73±10.654 | P3-P6 months | −2.700 9.102 −1.625 0.115 |
| **LDL** | | | | |
| Pre | 115–197 | 150.43±21.633 | P-P3 months | 28.767 14.880 10.589 <0.001* |
| Post 3 months | 101–143 | 126.67±14.019 | P-P6 months | 48.200 19.379 13.623 <0.001* |
| Post 6 months | 80–143 | 102.23±14.019 | P3-P6 months | 19.433 7.894 13.483 <0.001* |
| **TG** | | | | |
| Pre | 99–151 | 127.96±15.048 | P-P3 months | 1.367 2.822 2.652 0.013* |
| Post 3 months | 100–148 | 126.60±14.827 | P-P6 months | 1.300 5.154 1.382 0.178 |
| Post 6 months | 92–149 | 126.66±15.584 | P3-P6 months | −0.067 4.135 −0.088 0.930 |
| **T. CH** | | | | |
| Pre | 191–268 | 231.30±21.963 | P-P3 months | 17.333 8.965 10.590 <0.001* |
| Post 3 months | 175–253 | 213.96±22.483 | P-P6 months | 28.700 12.058 13.037 <0.001* |
| Post 6 months | 162–237 | 202.60±23.986 | P3-P6 months | 11.367 8.954 6.953 <0.001* |
| **DBP** | | | | |
| Pre | 70–100 | 85.50±7.234 | P-P3 months | 3.667 2.604 7.712 <0.001* |
| Post 3 months | 70–90 | 81.83±5.943 | P-P6 months | 7.167 4.857 8.082 <0.001* |
| Post 6 months | 70–85 | 78.33±5.142 | P3-P6 months | 3.500 3.256 5.887 <0.001* |

COMP., comparison; P, pre; P3, post 3 months; P6, post 6 months. Numerical variables are presented as mean and SD. Used test: paired t test (for normally distributed data). p value >0.05 nonsignificant. * p value ≤0.05 significant. ** p value <0.01 highly significant.
Also, a statistically significant difference between LDL level before, 3 months and 6 months after levothyroxine treatment was shown with \( p \) value \(<0.001\) for both, with mean \((121.667 \pm 13.949, 102.233 \pm 14.019)\) mg/dL, respectively.

In addition, there was a statistically significant difference between triglycerides level before and 3 months after levothyroxine treatment with \( p \) value \(0.013\), with mean \((126.600 \pm 14.827)\) mg/dL, while there is no significant difference between triglycerides level before and 6 months after levothyroxine treatment. Also, there was a significant difference between total cholesterol level before, 3 months and 6 months after levothyroxine treatment with \( p \) value \(<0.001\) for both, with mean \((213.967 \pm 22.483, 202.600 \pm 23.986)\) mg/dL, respectively (Table 3).

Comparison between results before, 3 months and 6 months after treatment regarding carotid intima-media thickness and level of cognitive impairment assessed by Addenbrooke’s questionnaire. This table showed that there is a statistically significant reduction in carotid intima-media thickness when comparing data before, 3 months and 6 months after levothyroxine treatment with \( p \) value \(<0.001\) for both, with mean \((0.941 \pm 0.150, 0.901 \pm 0.138)\) mm, respectively. Additionally, there was a statistically significant improvement in cognitive impairment before, 3 months and 6 months after levothyroxine treatment represented by improvement in Addenbrooke’s questionnaire results with \( p \) value \(<0.001\) for both, with mean \((91.300 \pm 1.264, 93.867 \pm 2.751)\), respectively.

Correlation between TSH level and mild cognitive impairment assessed by Addenbrooke’s questionnaire before treatment with levothyroxine showed a considerable inverse relation between TSH level and mild cognitive impairment before treatment with \( r \) value \((-0.365)\) as when TSH increased, results of Addenbrooke’s questionnaire decreased (low score) so, cognitive impairment increased (Table 4).

Correlation between TSH level and mild cognitive impairment assessed by Addenbrooke’s questionnaire after 3 months of treatment with levothyroxine showed that there is a remarkable inverse relation between TSH level and mild cognitive impairment after 3 months of treatment with levothyroxine with \( r \) value \((-0.383)\) as when

**Table 3.** Comparison between results before, 3 months and 6 months after treatment regarding carotid intima-media thickness and level of cognitive impairment assessed by Addenbrooke’s questionnaire

| Time          | Range     | Mean ± SD         | COMP.       | Differences mean ± SD | Paired test t | \( p \) value |
|---------------|-----------|-------------------|-------------|-----------------------|---------------|--------------|
| Carotid intima-media thickness |           |                   |             |                       |               |              |
| Pre           | 0.63–1.21 | 0.993±0.168       | P-P3 months | 0.052 ± 0.031         | 9.170         | <0.001*      |
| Post 3 months | 0.63–1.17 | 0.941±0.150       | P-P6 months | 0.092 ± 0.048         | 10.493        | <0.001*      |
| Post 6 months | 0.63–1.11 | 0.901±0.138       | P3-P6 months| 0.040 ± 0.034         | 6.539         | <0.001*      |
| Addenbrooke’s questionnaire |           |                   |             |                       |               |              |
| Pre           | 89–93     | 90.000±1.145      | P-P3 months | −1.300 ± 1.291        | −5.517        | <0.001*      |
| Post 3 months | 89–94     | 91.300±1.264      | P-P6 months | −3.867 ± 3.048        | −6.948        | <0.001*      |
| Post 6 months | 89–98     | 93.867±2.751      | P3-P6 months| −2.567 ± 2.096        | −6.708        | <0.001*      |

COMP., comparison; P, pre; P3, post 3 months; P6, post 6 months. Used test: paired \( t \) test Numerical variables are presented as mean and SD. * Indicates significance of \( p \) value.

**Table 4.** Shows correlation between TSH level and mild cognitive impairment assessed by Addenbrooke’s questionnaire before treatment with levothyroxine and 3, 6 months after treatment

| Correlations | Addenbrooke’s questionnaire pre | \( R \) | \( p \) value |
|--------------|--------------------------------|--------|--------------|
| TSH pre      | −0.365                         | 0.047* |
| Correlations | Addenbrooke’s questionnaire post 3 months | \( R \) | \( p \) value |
| TSH post 3 months | −0.383                       | 0.037* |
| Correlations | Addenbrooke’s questionnaire post 6 months | \( R \) | \( p \) value |
| TSH post 6 months | −0.378                       | 0.039* |

Used test: Pearson’s correlation coefficient. * Indicates significance of \( p \) value.
TSH decreased, results of Addenbrooke’s questionnaire increased so, cognitive impairment improved (Table 4). Correlation between TSH level and mild cognitive Impairment assessed by Addenbrooke’s questionnaire after 6 months of treatment with levothyroxine showed that there is a considerable inverse relation between TSH level and mild cognitive impairment after 6 months of treatment with levothyroxine with r value (−0.378) as when TSH decreased, results of Addenbrooke’s questionnaire increased so, cognitive impairment improved (Table 4).

Discussion

TSH levels above the upper limit of normal and normal serum-free thyroxine levels describe SHT [9]. The prevalence of SCH in the adult population is roughly 4–10 percent, but this varies by population, with more cases in iodine-sufficient locations [10].

Thyroid medication users are more likely to develop the condition. SCH, like other thyroid disorders, is more frequent in women than in males and gets worse with age. Every year, about 2–5 percent of SCH patients will develop overt hypothyroidism [11].

Cognitive function denotes the way a person processes thoughts. Memory, speaking, reading comprehension, and the ability to learn new things are all parts of cognition, and hypothyroidism affects cognitive functioning and mood [6].

Thyroid hormone influences the development of the central nervous system. Thyroid hormone also plays an important part in adult brain processes; however, the mechanism that specifies this involvement should be explored [12].

Thyroid hormone shortage slows all cognitive activities, including speaking. Loss of initiative, sluggishness, memory problems, lethargy, and somnolence are all symptoms. Although the pattern is diverse and complete recovery is not required, these neuropsychiatric symptoms improve with treatment and return to a euthyroid state [13].

The aim of our study was to detect the effect of levothyroxine on cognitive impairment in patients with SHT. Our study shows that total number of patients were 30, 23 of them were females representing about 76.67% of all participants and 23.33% (7 male patients). On the other hand, 11 patients (36.67%) of them had goitre and 19 patients (63.33%) of them had normal neck US.

These results come in line with several studies by Gussekloo et al [14], Walsh et al. [15], and Iervasi et al. [16], which showed a higher incidence in women (30–66%) than in men. The cause of female dominance is unknown. Hormone replacement therapy raised the levels of thyroid-binding protein and TSH in one research of postmenopausal women, implying that oestrogen is a risk factor [17].

Our study shows that there is increased body weight among study group, these results are in harmony with Kitahara et al. [18], who found a link between body mass index and an increase in TSH level even after controlling for age, menopausal status, and smoking. Conversely to our results, Dall’asta et al. [19] suggested that TSH levels fell because of losing weight. The increase in TSH resulted in an increase in weight of 1.1 kg in males and 2.3 kg in women.

In our study, an increase in blood pressure was observed among study group; these results come in line with a study by Liu et al. [20], where their investigation found that SHT may increase the risk for hypertension. These findings differ from those of Walsh et al. [15] and Duan et al. [21], who found no link between SHT and a rise in blood pressure. This lack of correlation could explain why case-control studies have fewer patients or why Walsh et al.’s [15] study had selection bias due to the clinic-based approach. Differences in race, lifestyle, and genetic background of the sample study are other possibilities. There has been no universally accepted explanation.

Our study shows that there is effect of SHT on lipid profile with increase in total cholesterol, LDL, triglycerides, and reduction in HDL. The results are in agreement with a meta-analysis study by Liu et al. [22], which included total number of 41,931 adults, among whom 4,526 were identified as subclinical hypothyroid patients and 37,405 as having a status of euthyroid, suggested that the serum total cholesterol, LDL, and total triglyceride levels were increased in patients with SHT compared with euthyroid individuals, with no significant difference for HDL.

Also, these results are agreeing with a study conducted in Colorado with a population sample of 25,862 people [10] in which patients with SHT exhibited greater total cholesterol values than euthyroid people. In the NHANES III cohort, however, cholesterol and triglycerides were greater in patients with SHT than in euthyroid subjects, but these differences were lost after controlling for sex, race, age, and lipid-lowering medication use [23].

In our study, we found that there is increase in carotid intima-media thickness; these results go in line with a meta-analysis study by Gao et al. [24], which included 3,602 patients, showed higher carotid IMT in patients with
SCH compared with euthyroid patients. In our study, there was a significant reduction in weight after treatment in comparison to before treatment, which agrees with prospective open-label study by Pandrc et al. [25], which was on 35 patients with SCH about psychosomatic effects of levothyroxine. In Pandrc study, patients were given levothyroxine for 3 months until euthyroid state. The treatment resulted in body weight decrease ($p$ value = 0.030).

Diuresis and weight loss are common early responses to levothyroxine replacement, resulting in the mobilization of interstitial fluid as glycosaminoglycans. Even in obese patients, weight loss is extraordinarily high, exceeding 5 kg, especially if pretreatment TSH concentrations were only modestly increased, as demonstrated by McDermott [26].

In our study, we found that a significant reduction of systolic and diastolic blood pressure after treatment with levothyroxine with $p$ value <0.001. Those results come in line with a meta-analysis study by He et al. [27] on 19 prospective follow-up studies found that levothyroxine therapy effect on SBP and DBP showed significant decrease by 4.80 mm Hg and 2.74 mm Hg, respectively, with $p$ value < 0.001 for both.

According to certain research, a higher TSH level is linked to poor endothelial function, renal vascular resistance, and arterial stiffness, all of which can lead to an increase in blood pressure [28]. These data suggest that TSH may have a role in the development of hypertension. The effect of restoring TSH levels to normal on lowering blood pressure with LT4 medication in SCH patients was demonstrated in this study, bolstering the hypothesis that elevated TSH levels play a role in the development of hypertension.

Our study concluded that there is significant lowering effect of levothyroxine on T. cholesterol and LDL levels with $p$ value <0.001 for both. With significant increase in HDL level with $p$ value = 0.001 but no significant decrease on triglyceride level. This comes in line with a meta-analysis study of 12 randomized controlled trials on 940 participants by Li et al. [29], stated that levothyroxine treatment yielded a reduction in TC and LDL with no significant effects on HDL or triglycerides.

Thyroid hormones reduce cholesterol mainly through increase in expression of LDL-cholesterol receptors in the liver and peripheral organs [30]. In our study, there was a significant reduction of carotid intima-media thickness after levothyroxine treatment with $p$ value <0.001, which agrees with a meta-analysis study by Zhao et al. [30] on 117 patients indicating that levothyroxine treatment of SCH patients can reduce Carotid IMT, maybe as a result of reduced total cholesterol, triglyceride, low-density lipoprotein, SBP, DBP.

Contrary to our study, Cabral et al. [31] reported that there is no significant change in mean carotid IMT after 12 months of levothyroxine therapy. In our study, we found a significant improvement in cognitive function of patients with SHT after treatment with LT4 using Addenbrooke’s questionnaire with $p$ value < 0.001. Those results come in line with a double-blind placebo-controlled clinical trial by Aghil et al. [32], which was conducted on 60 patients with SHT demonstrated the effectiveness of LT4 for cognitive function of patients with SHT.

Our study has illustrated that there was a significant reverse relation between TSH level and cognitive function with $p$ value = 0.047 when TSH increased, results of Addenbrooke’s questionnaire decreased so cognitive impairment increased. Those results come in agreement with study by Bajaj et al. [33] on 103 diagnosed SHT cases with cognitive impairment by MMS examination was found in 33 (30.9%), whereas it was found in only 15 (14.54%) out of 103 controls ($p = 0.003$), incidence of cognitive impairment was significantly higher in SHT as compared to controls. Presence of cognitive impairment related to TSH level, as TSH increased cognitive function decreased.

Our results are also in agreement with Elbadawy et al. [34], who found that there is a close relation between thyroid hormones and cognitive dysfunction. Serum FT3 levels decreased, whereas the serum TSH level increased with the decrease in cognitive function. Also, the TSH level had a negative correlation with the MMS examination scores. So, recommended that thyroid function was associated with cognitive impairment through subcortical ischemic vascular dementia. Contrary to our study, a meta-analysis study by Rieben et al. [35] found no relation between SHT and risk of dementia. One of the hypotheses which can explain the probable mechanism is that there are numerous nuclear thyroid hormone receptors in the hippocampus and frontal lobes, T3 binds to these nuclear receptors, and these brain areas are well-known centers for memory and cognition [36].

The majority of T3 in the brain comes from deiodinases in the tissue, which have crucial effects on thyroid hormone function due to their distribution and control. In the brain, deiodinase 2 (D2) and deiodinase 3 (D3) are both expressed. T4 is inactivated by conversion to reverse T3, and T3 is converted to di-iodothyronine (T2) by D3, whereas T4 is converted to T3 by D2. D2 is primarily expressed in glial cells throughout the CNS and plays an important role in its development and function [37].
Low levels of local T3 synthesis in the brain may be caused by polymorphisms in the D2 genes. Thyroid hormone affects mood and cognition through a variety of processes. Many structures in the limbic system have been implicated in the development of mood disorders. In addition, the interaction of thyroid function with the brain neurotransmitter system, such as norepinephrine and serotonin, which are known to play a big part in mood and behavior control, may play a role in brain development and maturity [37].

Conclusion

This study showed that SHT has a great effect on cognitive impairment, as normalization in TSH level results in improvement of cognitive function. Also, showed that there is a statistically significant relation between SHT and carotid IMT. After levothyroxine therapy, results showed a significant reduction in carotid IMT in comparison to pretreatment ranges.

Our study also showed that there is statistically significant improvement after treatment with levothyroxine regarding lipid profile, weight, and BMI. The current study showed the effect of levothyroxine treatment on mild cognitive impairment after 6 months; 19 patients (63.33%) had improvement in cognition after treatment with levothyroxine.

SHT has a great effect on cognitive impairment. Normalization in TSH level results in improvement in cognitive function. Also, a statistically significant relation was found between SHT and carotid intima-media thickness which may share in improvement of cognitive function. Our study also showed that treatment with LT4 has a great improvement on lipid profile which in turn positively affects cardiac and cognitive function.

Statement of Ethics

This study has been approved by the Ain Shams University, Faculty of Medicine, Research Ethics Committee. All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional and National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed written consent was obtained from all individual participants included in the study. Approval number: FMASU M S 511/2020. Study approval reference date: 4/8/2020.

Conflict of Interest Statement

The authors declare no conflicts of interest, financial or otherwise.

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Author Contributions

Salwa Seddik Hosny El-khwaga, Nahla Nader Adly, and Ahmed Mohamed Bahaaeldin contributed to design of the work, drafting of the work, final approval of the manuscript for publication, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Dina Ahmed Marwan participated in analysis of data of the work, revising it critically, final approval of the version, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Marina El-Amir Hakim added the following to this work: interpretation of data of the work, drafting the work, final approval of the version, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author, AMB (email address: ahmedbahaa@med.asu.edu.eg) upon reasonable request.

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