Changes of subtests of Wechsler Memory Scale and cognitive function in subjects with subclinical hypothyroidism following treatment with levothyroxine

Rokhsareh Aghili, Mohammad E. Khamseh, Mojtaba Malek, Ali Hadian, Hamid R. Baradaran, Laily Najafi, Zahra Emami

Endocrine Research Center (Firouzgar), Institute of Endocrinology and Metabolism, Tehran University of Medical Sciences (TUMS), Tehran, Iran

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Corresponding author:
Dr. Laily Najafi MD
Endocrine Research Center (Firouzgar)
Institute of Endocrinology and Metabolism
Tehran University of Medical Sciences (TUMS)
Firouzgar Alley
Valadi St., Behafarin St.,
Karimkhan Ave., Vali- Asr Sq.
15937-48711, Tehran, Iran
Phone: 0098 21 88945172, 0098 21 88945247
Fax: 0098 21 88945173
E-mail: l-najafi@farabi.tums.ac.ir, l.najafi@yahoo.com

Abstract

Introduction: Subclinical hypothyroidism has been reported to be associated with disturbed cognitive function. In this study, changes of subtests of the Wechsler Memory Scale and memory quotient were investigated in subjects with subclinical hypothyroidism following treatment with levothyroxine. The aim of the study was a randomized double blind placebo-controlled clinical trial.
Material and methods: Sixty subjects (51 females and 9 males) with subclinical hypothyroidism were enrolled. Memory quotient was evaluated at the beginning of the study and three months after enrollment, using Wechsler's memory test. Subclinical hypothyroidism was defined as serum TSH level between 4.5 mU/l and 10 mU/l in the presence of normal free-T4 (0.8-2 ng/dl) and positive anti-TPO-Ab. The intervention and control groups received levothyroxine and placebo respectively for 3 months. Re-evaluation was done using the Wechsler Memory Scale at the end of the study.
Results: The mean age was 34 ±10 years, mean TSH level was 8.25 ±3.64 muIU/l. Memory quotient was similar in both groups at the beginning of the study: 105.70 ±2.1 in intervention group vs. 105.87 ±2.1 in control group ($p = 0.89$). At the end of the study, the memory quotient rose by 9.3 points in the intervention group and by 3.23 in the controls ($p = 0.002$). Analysis of the scores of Wechsler Memory subtests in the intervention group indicated significant improvement of mental control ($p = 0.002$), logical memory ($p < 0.001$), associate learning ($p = 0.014$), age corrected score ($p = 0.002$), and memory quotient ($p < 0.001$).
Conclusions: This study showed the efficacy of levothyroxine for cognitive function of subjects with subclinical hypothyroidism.

Key words: Memory Quotient, Subclinical Hypothyroidism, Wechsler Memory Test, levothyroxine.

Introduction

Subclinical hypothyroidism (SCH) is defined biochemically as a normal serum free thyroxin (T4) concentration in the presence of increased thyroid stimulating hormone (TSH). One of the criteria to begin treatment in these subjects is probable progression of the disease to clinical hypothyroidism, which accounts for 3-8% of cases per year [1]. Higher titers of antithyroperoxidase (TPO) antibody and TSH levels are reported to be associated with disease progression [2]. Subclinical hypothyroid subjects are

usually asymptomatic. Clinical manifestations differ based on age, duration, and severity of hormone shortage and are usually non-specific [2, 3].

There are some concerns regarding prolonged levothyroxine treatment such as increased risk of osteoporosis, atrial fibrillation, and coronary artery disease. However, it has been shown that bone metabolism and body composition are not altered by levothyroxine treatment [4, 5]. Furthermore, the cardiovascular benefits of levothyroxine therapy outweigh its possible risks [6]. In addition, the role of thyroid hormone in cognitive organization has been proved [7]. Frank hypothyroidism is known to induce neurological and mental dysfunction but the effect of subclinical hypothyroidism on cognition and mental function is controversial. Cognition refers to mental processes that include storage, remembering, and using information.

Cognitive disorders can affect various activities such as receiving, resembling, memory, persuading, problem solving, decision making, and language [8]. Subclinical hypothyroidism may be associated with a defect in verbal memory and executive function which is due to abnormal function of the hippocampus [7, 9]. Wechsler's memory test has been used as a valid tool to evaluate memory. The Wechsler Memory Scale (WMS) is a neuropsychological test designed to measure different memory functions. It is appropriate for studying logical memory, mental control, visual reproduction, associate learning, working memory and immediate memory. This test is simple and rapid and provides reliable information regarding organic and functional memory disorders. Wechsler's memory test considers the different memory power at different ages. The final score is computed according to the WMS manual which yields the percentile-rank score adjusted for age [10]. In this study, changes of subtests of the Wechsler Memory Scale and memory quotient were investigated in subjects with subclinical hypothyroidism following treatment with levothyroxine.

Material and methods

This study was a randomized double blind placebo-controlled clinical trial. Sixty subjects (51 females and 9 males) referring to the outpatient thyroid clinics with subclinical hypothyroidism between 18 and 64 years old with non-specific symptoms of hypothyroidism such as weight gain, dry skin, fatigue, muscle cramp, hoarseness, constipation, and irregular menstruation were enrolled in this study. Subjects who had a history of endocrine or autoimmune diseases other than hypothyroidism, myxedema coma, proven psychiatric disorder, pregnancy or lactation, intake of thyroid hormones or corticosteroids in the previous 2 months were excluded from the study. All eligible subjects agreed and signed the consent form after full explanation of the purpose and nature of all procedures used. They were randomly allocated to two groups using a simple randomization method. The control group comprised 25 females and 5 males (mean age: 36.07 years, range: 21-58 years) and the intervention group consisted of 26 females and 4 males (mean age: 32.37 years, range: 19-53 years). Memory quotient of the participants was evaluated at the beginning of the study and three months after enrollment using Wechsler's memory test. Subjects were submitted to the Wechsler Memory Scale; their ratings on the neurobehavioral tests and their thyroid hormone profile were compared to the age- or sex-matched controls. Cognitive functioning was evaluated using the Wechsler Memory Scale, designed to assess learning, memory and working memory. Seven subtests are included in the test: information, orientation, mental control, logic memory, digits forward and backward, visual reproduction and associate learning. The WMS provides a total "memory quotient" (MQ) that accounts for age-related mnemonic variability. Subclinical hypothyroidism was defined as serum TSH level between 4.5 mU/l and 10 mU/l in the presence of normal free-T4 (0.8-2 ng/dl) and positive anti-TPO-Ab. Subjects who had diabetes mellitus, heart failure, chronic liver or pulmonary disorder, history of head trauma, seizure, known psychological or mental disorders and pregnancy were excluded. All eligible subjects filled out the Wechsler Memory Scale at the beginning of the study. The intervention group received 100 µg of levothyroxine (Iran Hormone Product) and the control group received placebo for 3 months. The participants were asked to bring the remaining tablets to assess compliance. The subjects were re-evaluated by the Wechsler Memory Scale at the end of the study.

This project was accepted by the ethical committee of Tehran University of Medical Sciences; ethical code: 13/2/1390.

Statistical analysis

Data were analyzed using SPSS software version 18. For comparison of mean age, TSH, FT4 and T4 between two groups Mann-Whitney U test was used. *T*-test was applied to compare mean memory quotient between groups and paired *T*-test to compare these values before and after intervention. Independent sample *T*-test was used for comparison of mean memory quotient variable. Simple Pearson regression test was used to investigate the relationship between memory quotient variable and TSH variability.

Results

In this study, 60 subclinical hypothyroid subjects were divided randomly into two equal groups.

Table I. Baseline characteristics of participants

Variables	Intervention group*	Control group*	Value of *p*
Age [years]	32.37 ±11.35	36.07 ±11.35	0.4
TSH [ml/l]	8.29 ±4.9	8.12 ±3.12	0.9
FT4 [ng/dl]	1.38 ±0.26	1.37 ±0.29	0.83
T4 [mg/dl]	7.38 ±1.37	7.41 ±1.48	0.92

**Data are shown as mean ± SD*

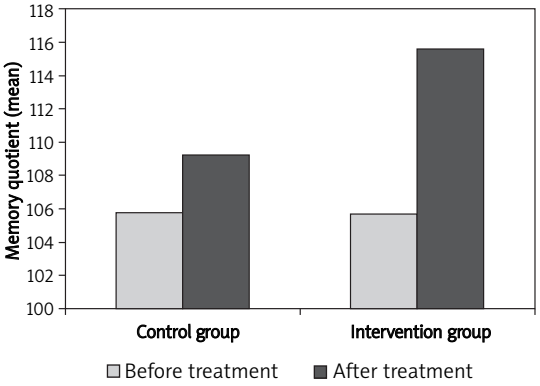

Figure 1. Comparison of memory quotient mean in the intervention and control groups

The mean age of the participants was 34 ±10 years and 85% of them were female (51). Forty-three subjects were married. There were no statistical differences in WMS subtests and memory quotient (p = 0.31) between the two groups at the beginning of the study. Demographic variables and MQ scores were compared. Baseline characteristics of the participants are shown in Table I. Thyroid hormone parameters were similar in both groups at the beginning of the study, as shown in Table I. The changes in biochemical parameters before and after the treatment are shown in Table II. Table III shows the clinical symptomatology of subclinical hypothyroidism in both groups before and after treatment. Each individual's score on memory was computed according to the WMS manual, which yields the percentile-rank score adjusted for age.

At the end of the study, TSH levels were normalized in all subjects in the intervention group (Table II). Moreover, there was no TSH suppression indicating subclinical hyperthyroidism in this group. In addition, the memory quotient rate increased from 105 ±2.8 to 115 ±2.6 (ΔMQ = 9.9 ±1.46) in the intervention group and from 105.87 ±2.09 to 109 ±2.5 (ΔMQ = 3.2 ±1.39) in the control group (p = 0.002). In Figure 1, comparison of the memory quotient mean is illustrated for the intervention and control groups before and after treatment.

The result for the subtests of WMS in the intervention group showed that the mental control (p = 0.002), logical memory (p < 0.001), associate learning (p = 0.014), age-corrected score (p = 0.002), and memory quotient (p < 0.001) improved significantly after treatment. Scores of Wechsler Memory Scale subtests of the intervention group at baseline and after levothyroxine treatment are shown in Table IV.

A significant inverse relationship was detected between TSH level and memory quotient (R = –0.39).

Table II. Biochemical parameters before and after treatment

Variables	Intervention group			Control group		
	Baseline*	Final*	Value of *p*	Baseline*	Final*	Value of *p*
TSH [ml/l]	8.3907 ±4.091	2.0070 ±1.34	< 0.001	8.1203 ±3.20	7.8270 ±5.17	0.733
T4 [mg/dl]	7.3880 ±1.375	8.6077 ±2.058	0.004	7.4703 ±1.48	8.1363 ±1.98	0.093

**Data are shown as mean ± SD*

Table III. Frequency of non-specific symptoms of subclinical hypothyroidism in the intervention and control groups

Symptoms	Intervention group			Control group		
	Before treatment*	After treatment*	Value of *p*	Before treatment*	After treatment*	Value of *p*
Weight gain	17 (56.7%)	10 (33.3%)	0.118	16 (53%)	9 (30%)	0.065
Dry skin	13 (43.3%)	9 (30%)	0.344	14 (46.7%)	11 (36.7%)	0.45
Fatigue	25 (83.3%)	23 (76.7%)	0.4	25 (83.3%)	24 (80%)	1
Muscle cramp	19 (63.3%)	15 (50%)	0.34	17 (56.7%)	15 (50%)	0.77
Hoarseness	5 (16.7%)	3 (10%)	0.6	4 (13.3%)	4 (13.3%)	1
Constipation	7 (23.3%)	4 (13.3%)	0.5	10 (33.3%)	7 (23.3%)	0.3
Irregular menstruation	11 (36.7%)	9 (30%)	0.7	24 (80%)	24 (80%)	1

**Data are shown as n (%)*

Table IV. Baseline and final scores of Wechsler Memory Scale subtests for the intervention and control groups

WMS Subtests	Intervention group			Control group		
	Baseline score*	Final score*	Value of *p*	Baseline score*	Final score*	Value of *p*
Information	5.88 ±0.34	5.78 ±0.49	0.26	5.7 ±0.54	5.7 ±0.54	1.00
Orientation	4.53 ±0.67	4.66 ±0.6	0.25	4.4 ±0.7	4.3 ±0.73	0.62
Mental control	8.03 ±0.99	7.35 ±1.33	0.002	6.4 ±0.97	7.04 ±1.2	0.024
Logical memory	10.83 ±2.94	12.31 ±2.32	< 0.001	9.5 ±1.9	10.2 ±2.6	0.14
Digits forward and backward	8.9 ±1.44	8.48 ±1.6	0.11	8.18 ±1.7	8.18 ±1.5	1.00
Associate learning	7.1 ±2.47	12.9 ±1.53	0.014	16.8 ±2.1	16.7 ±2.5	0.76
Visual reproduction	12.9 ±1.53	12.37 ±1.62	0.13	13.3 ±1.3	12.03 ±1.6	0.003
Age-corrected score	105 ±2.8	115 ±2.6	0.002	101.27 ±6.9	100.6 ±6.6	0.4
Memory quotient	101.45 ±7.34	107.03 ±7.44	< 0.001	106.4 ±12.1	105.4 ±12.06	0.5

**Data are shown as mean ± SD*

Memory quotient significantly improved in subjects after levothyroxine treatment in comparison with subjects taking placebo ($p = 0.002$).

Discussion

This study indicated that memory quotient improved significantly in subclinical hypothyroid subjects after treatment with levothyroxine. Meanwhile, there was also significant improvement in some Wechsler Memory Scale subtests such as mental control ($p = 0.002$), logical memory ($p < 0.001$), and associate learning ($p = 0.014$). The improvement of memory quotient remained significant after adjustment of the scores for age ($p < 0.001$).

Thyroid hormone plays a major role as a regulator of nervous system myelination, growth, puberty, metabolism, and organ functions [8]. Thyroid function disorder is a graded phenomenon [11]. Subclinical hypothyroidism represents an early stage of thyroid disease which progresses to overt hypothyroidism by 3-18% per year, especially in the elderly [12, 13]. The risk factors of progression are the presence of antithyroid antibodies, serum TSH of more than 20 µU/ml, history of radioiodine therapy or external radiation and lithium therapy [14]. There is increasing evidence suggesting that mild (subclinical) thyroid disorders may be potential contributors to significant clinical conditions [11]. The overall prevalence of SCH has been reported as 7-26% in the elderly [15] and 3% to 7% in the middle aged population [16]. There has been considerable controversy regarding the clinical significance of this condition and its management. Due to considerable morbidity, the general consensus is to treat selected subjects with early thyroid failure [17]. The degree to which subclinical hypothyroidism affects mood and cognitive functions and whether these symptoms respond to treatment remains controversial. Most studies support a relationship between thyroid function and cognition, particularly poor learning, reduced information processing speed, and efficiency in executive functions [18].

Three cross-sectional studies confirmed mild functional learning disorder and memory problems in young subjects with subclinical hypothyroidism [19-21]. In addition, association of Alzheimer disease and subclinical hypothyroidism has been reported in a population-based study [22]. Improvements of memory performance, frontal executive functions, and some aspects of cognitive performance have been observed after treatment of subclinical hypothyroidism subjects with levothyroxine [23-25].

Quijano *et al.* conducted a survey that included 15 subclinical hypothyroid subjects and 15 mild clinically hypothyroid subjects. At enrollment, mild clinically hypothyroid subjects showed worse cognitive status in comparison with the subclinical hypothyroid group but after treatment both groups showed normal cognitive status [19]. In another study performed by Monzani *et al.* comparison was carried out in SCH between pretreatment ratings and those obtained following 6-month L-thyroxin treatment which indicated a significant improvement in subjects' memory skills as evaluated by Wechsler Memory Scale (memory quotient (MQ) = 99.9 ±4.0; $p = 0.002$ (treated vs. untreated)) [26]. Improvement of MQ following levothyroxine treatment has been reported in small series of subclinical hypothyroidism subjects as well [7, 27].

On the other hand, some studies have indicated that levothyroxine treatment has no beneficial effect on cognitive function in subclinical hypothyroidism, either in the total memory scale or in the subtests of WMS. Parle *et al.* [28] examined the effect of LT4 treatment in 94 subjects with subclinical hypothyroidism in a randomized placebo-controlled blinded clinical trial. They used stan-

dard tests of cognition at baseline and at 6 and 12 months after treatment and found no difference in cognitive function between the 2 groups. However, the major limitations of this study were the type of cognitive assessment measures which detect gross impairment of cognition, and the low number of placebo-treated subjects who completed the study. In another study conducted by Jorde *et al*. [29], detailed cognitive testing was done at baseline and 12 months after treatment with LT4 or placebo. There was no difference between the groups at baseline. Furthermore, LT4 treatment had no effect on the outcome measures. This study was limited by the relatively mild degree of subclinical hypothyroidism.

In another double blind clinical trial, on 23 subclinical hypothyroid subjects, immediate and late memory, and psychomotor activity did not improve after treatment. However, the Kaflen test was used for evaluation of cognitive function in the study [30].

It should be mentioned that the discrepancies among the studies regarding the effect of levothyroxine on cognitive function of SCH subjects might be due to different tools used for the assessment of cognitive function as well as the small sample size of the populations being studied [24, 25].

Considering Wechsler Memory Scale subtests, our study showed significant improvement in mental control, logical memory, and associate learning. However, information, orientation, digits forward and backward, and visual reproduction did not change significantly. Considering the improvement of memory quotient in this study, it seems that mental control, logical memory, and associate learning might have a more influential effect on cognitive function. In another study conducted by Jenovsky *et al*., significant improvement of verbal ($p < 0.01$), visual ($p < 0.05$), and total memory ($p < 0.01$), after levothyroxine treatment compared to placebo in SCH subjects was observed [16]. Nystrom *et al*. found that four of 17 women with subclinical hypothyroidism exhibited significant improvement on at least two of the neuropsychological measures following treatment with levothyroxine (150 µg/day) in a placebo-controlled, crossover, 2 × 6 month study [31]. Administration of levothyroxine (100-150 µg/day for 6 months) has also been shown to have beneficial effects on verbal and visual recall in 14 subjects with subclinical hypothyroidism [26].

There are some impressive strengths of this study. All the recruited subjects completed the trial. Moreover, TSH levels in all subjects in the intervention group were normalized (TSH < 4.5 mU/l) by the end of the study and no TSH suppression was observed in the levothyroxine group.

There are, however, some limitations to the study. The study might not have sufficient ability to detect the differences between the groups in certain subscales of cognitive function due to the small sample size. We were also unable to analyze the effect of race/ethnicity or social economic status due to the limited sample size and limitation of facilities.

In conclusion, this study showed the efficacy of levothyroxine on cognitive function of subjects with subclinical hypothyroidism, including mental control, logical memory, associate learning and visual reproduction.

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