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The effect of levothyroxine treatment in individuals with subclinical hypothyroidism on surrogate markers of atherosclerosis: a meta-analysis of randomized controlled trials

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ABSTRACT

Introduction: Subclinical hypothyroidism is associated with increased carotid intima media thickness (CIMT) and decreased flow-mediated dilation (FMD) – surrogate markers of subclinical atherosclerotic cardiovascular disease (ASCVD). However, treatment with levothyroxine in this population remains controversial.

Methods: Electronic database search was conducted for all randomized clinical trials (RCTs) that evaluated the treatment of subclinical hypothyroidism on surrogate markers of subclinical ASCVD. The primary and secondary outcomes were the mean change of CIMT and FMD, respectively. We calculated the weighted mean differences (MDs) and 95% confidence intervals (CIs) using the inverse variance random-effects method for continuous data.

Results: Seven RCTs were identified with a total of 541 patients. There were 115 males and the mean age was 54.5 ± 18.7 years with mean baseline thyroid-stimulating hormone of 6.78 ± 2.5. There were no differences between levothyroxine-treated patients and placebo with regard to CIMT differences (MD −0.02; 95% CI −0.08–0.04; P = 0.49; I^2 = 59%). However, the levothyroxine-treated group was associated with significantly increased FMD compared with placebo (MD 1.61; 95% CI 1.21–2.01; P < 0.01; I^2 = 0%).

Conclusions: Among patients with subclinical hypothyroidism, levothyroxine treatment was associated with significant improvement in FMD but not CIMT. Large, adequately powered trials with long-term follow-up are needed.

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Subclinical hypothyroidism; carotid-intima media thickness; flow-mediated dilation; surrogate markers of atherosclerosis

1. Introduction

Subclinical hypothyroidism (SCH) is defined by the coexistence of a normal free thyroxine (FT4) level and a thyroid-stimulating hormone (TSH) level above the reference range of normal [1]. SCH has been associated with increased risk of coronary heart disease (CHD) events and CHD mortality [2]. There has been no study powered enough to evaluate the clinical cardiovascular outcomes of levothyroxine treatment in the subclinical hypothyroid patient population [3]. Several tests have been rigorously validated as surrogate markers of atherosclerosis and endothelial dysfunction. These include both carotid intima media thickness (CIMT), specific ultrasonographic measurements of the carotid artery, and flow-mediated dilation (FMD), an endothelium-dependent reactive hyperemia test usually performed on the brachial artery [4]. Improvement of atherosclerosis can be inferred by either a decrease in CIMT or an increase in FMD. Several randomized controlled trials (RCTs) examined the effect of levothyroxine treatment on these markers with conflicting results.

A meta-analysis in 2017 by Zhou et al included 3 RCTs (total number of patients = 117) and concluded that 6 months of levothyroxine treatment decreases CIMT in patients with subclinical hypothyroidism [5]. In 2018, Blum et al studied the effect of levothyroxine treatment on CIMT in the older population (i.e. 65 years and older) with SCH and concluded there was no impact on CIMT after treatment [3]. This RCT was nested within the Thyroid hormone Replacement for Untreated older adults with Subclinical hypothyroidism (TRUST) trial [6]. Despite being the largest multinational RCT examining levothyroxine treatment in the elderly population with SCH, the TRUST trial was not powered enough to detect a difference in the clinical cardiovascular outcomes [3]. Therefore, we conducted this study to evaluate the effect of levothyroxine supplementation on the surrogate markers of atherosclerotic disease.

2. Methods

We conducted the meta-analysis according to the Preferred Reporting Items for Systematic Reviews and

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Meta-Analyses Protocols (PRISMA-P) Statement 2015. Three authors (BS, MM, SS) independently performed a literature search of PubMed/MEDLINE, Embase, and Scopus from inception to July 2018. A fourth author (BK) was consulted for any disagreements. We used Boolean operators for connections of the following headings: subclinical hypothyroidism, CIMT, carotid intima-media thickness, carotid artery intima-media thickness, endothelium, endothelial, IMT, atherosclerosis, carotid plaque. We included only RCTs that examined the association of SCH treatment with atherosclerotic disease markers.

BS, MM, and SS extracted the data and TH was consulted for any discrepancies. From each RCT, we extracted baseline characteristics (Table 1) and clinical outcomes (Table 2) used for the analysis. The primary outcome of the meta-analysis was the mean change of CIMT. The secondary outcome was FMD.

We calculated the weighted mean differences (MDs) and 95% confidence intervals (CIs) using the inverse variance method for continuous data. A random-effects model was used to account for the between-study heterogeneity. We assessed heterogeneity using I2 statistics. We performed sensitivity analysis for any significant heterogeneity by excluding trials successively. We analyzed our data using RevMan, version 5.3 Windows (Cochrane Collaboration, Oxford, UK).

3. Results

Our literature search for RCTs examining the effect of levothyroxine treatment on surrogate markers of endothelial dysfunction and atherosclerosis in patients with SCH concluded with seven RCTs. The total number of individuals was 541, and 21.3% (n = 115) were males. The mean age (± standard deviation (SD)) was 54.5 ± 18.7 years. The trials took place in Turkey, Brazil, and multiple countries in Europe. The range of follow-up period was from 3 to 15 months. Some trials included only female subjects. Thyroxine dose was adjusted periodically to achieve TSH within the normal range. Mean baseline TSH (±2 SD) was 6.78 ± 2.5 mIU/liter. Three of the RCTs used CIMT as the surrogate marker of atherosclerosis, while another three used FMD. One study measured both markers. The RCT done by Ersoy et al reported statistically significant improvement of CIMT after treatment but no absolute numbers were provided and therefore this study was not included in our final quantitative analysis [7]. There were no differences between levothyroxine-treated patients and placebo with regard to CIMT (MD −0.02; 95% CI −0.08–0.04; P = 0.49; I2 = 59%) (Figure 1). However, levothyroxine-treated patients were associated with significantly increased FMD compared with placebo (MD 1.61; 95% CI 1.21–2.01; P < 0.01; I2 = 0%) (Figure 2).

4. Discussion

In this meta-analysis of 541 total participants with subclinical hypothyroidism, we found that levothyroxine treatment was associated with a statistically significant favorable outcome on FMD but not CIMT. This is in contrast to the meta-analysis performed in 2017 by Zhou et al., which showed an overall improvement of CIMT with levothyroxine [5]. We believe the difference is mostly due to the significant weight of the recent study performed by Blum et al. in 2018, which concluded no significant improvement of CIMT [3]. Nevertheless, the Blum study was part of the TRUST trial, which was limited to older patients (mean age was 74.4 years) [6]. In addition, in 2017, Aziz et al performed a meta-analysis that was not limited RCTs and concluded that thyroxine treatment decreased CIMT and improved lipid profile in individuals with SCH [8].

Zhou et al. summarized the possible mechanisms of levothyroxine-dependent improvement of CIMT [5]. These include improvement of lipid profile, decreased activation of the TSH receptor in endothelial cells, and improvement of blood pressure. Moreover, Taddei et al. demonstrated reduction of endothelium-derived nitric oxide (NO) in patients with SCH and subsequent improvement of endothelium-dependent vasodilation after six months of euthyroidism [9].

According to the most recent guidelines from the American Thyroid Association (ATA) and the American Association of Clinical Endocrinology (AACE) published in 2012, patients with TSH levels higher than 10 mIU/L should be treated because of increased risk of heart failure and cardiovascular mortality (Grade B, best evidence level (BEL) 1). In addition, for patients with SCH and TSH less than 10 mIU/L, the treatment should be considered, especially for those with positive antibodies to thyroid peroxidase (TPOAb), hypothyroid symptoms, or with the evidence of atherosclerotic cardiovascular disease or heart failure (Grade B, BEL 1) [10].

Our study has limitations, including a low number of studies and events, different cut-off values for TSH, and relatively short durations of follow-up. Also, we did not perform a subgroup analysis based on gender, age, symptoms of hypothyroidism, or comorbid conditions.

5. Conclusion

In our meta-analysis, the treatment of subclinical hypothyroidism was associated with statistically significant improvement of FMD but not CIMT. Larger studies with longer durations of follow-up looking specifically at clinical cardiovascular outcomes of

Table 1. Baseline characteristics.

Author, Year		Age (yr)	Female Sex (n, %)	Race (n, %)	BMI (kg/m^2)	SBP (mm Hg)	DBP (mm Hg)	Current Smoking (n, %)	DM (n, %)	Prior CVD (n, %)	eGFR (ml/min)	TC (mg/dl)	LDL (mg/dl)
Blum, 2018	Treatment	74.5 ± 5.4	49 (45.0)	White 107 (98.2)	27.9 ± 5.3	137.6 ± 18.2	74.1 ± 11.2	8 (7.3)	17 (15.6)	26 (23.9)	-	196.4 ± 42.2	109.8 ± 38.3
	Placebo	74.6 ± 6.2	49 (45.4)	White 106 (98.2)	26.9 ± 4.6	138.5 ± 20.0	77.4 ± 12.3	10 (9.3)	11 (10.2)	30 (27.8)	-	200.3 ± 42.9	111.4 ± 36.0
Ersoy, 2012	Treatment	44.0 ± 11.6	29 (96.7)	-	30.1 ± 6.1	132.5 ± 19.0	79.8 ± 10.4	2 (6.6)	3 (10)	0	-	200.0 ± 32.5	114.2 ± 27.9
	Placebo	47.9 ± 14.6	29 (96.7)	-	28.7 ± 4.3	127.8 ± 18.8	73.7 ± 12.0	2 (6.6)	3 (10)	0	-	168.4 ± 37.7	92.6 ± 33.2
Cabral, 2011	Treatment	43.36 ± 9.8	14 (100)	-	25.89 ± 2.29	-	-	2 (14.3)	0	0	-	213.4 ± 53.1	137.9 ± 47.9
	OG	47.59 ± 8.4	18 (100)	-	26.24 ± 2.71	-	-	2 (11.1)	0	0	-	226.1 ± 43.5	147.5 ± 37.5
Duman, 2007		37.0 ± 12.6	60 (100)	-	25.1 ± 4.3	126 ± 13	77 ± 10	0	0	0	-	205 ± 27	124 ± 28
Razvi, 2007		53.8 ± 12.6	82 (82)	-	-	132.5 ± 21.5	79.9 ± 9.2	25 (25)	0	0	-	232.0 ± 46.4	139.2 ± 38.7
Duman, 2006	levothyroxine	37 ± 11	59 (100)	-	25.6 ± 4.2	-	-	0	0	0	-	204 ± 32	126 ± 32
	Simvastatin											210 ± 25	134 ± 26
	No treatment											206 ± 25	124 ± 28
Monzani, 2004	Treatment	37 ± 11	37 (82)	-	23.7 ± 3.5	112 ± 15	69 ± 9	0	0	0	-	191.6 ± 32.5	119.2 ± 27.8
	Placebo			-	24.9 ± 3.8	114 ± 13	72 ± 8	0	0	0	-	219.6 ± 48.9	141.3 ± 38.6

HDL (mg/dl)	TG (mg/dl)	Lipoprotein (a) (mg/dl)	ApoB (mg/dl)	ApoA (mg/dl)	TSH (mIU/liter)	Free T4 (ng/dl)	Free T3 (ng/L)	TPO-Ab (%)	Mean IMT (mm)	Maximal IMT (mm)	FMD (%)
56.1 ± 18.2	159.4 ± 100.1	-	-	-	6.40 ± 2.02	1.05 ± 0.16	-	-	0.85 ± 0.14	1.10 ± 0.22	-
57.6 ± 17.8	157.7 ± 77.1	-	-	-	6.51 ± 2.12	1.06 ± 0.15	-	-	0.82 ± 0.13	1.07 ± 0.18	-
52.9 ± 13.4	140.7 ± 81.8	-	-	-	7.5 ± 1.5	0.84 ± 0.13	2.88 ± 0.66	-	-	-	-
53.2 ± 10.9	113.5 ± 43.4	-	-	-	6.8 ± 1.4	0.86 ± 0.15	2.92 ± 0.64	-	-	-	-
56.78 ± 11.15	136.1 ± 119.2	61.8 ± 62.7	109.3 ± 44.2	150.2 ± 24.7	6.79 ± 2.0	0.97 ± 0.13	-	64.3	0.66 ± 0.11	-	16.81 ± 7.0
51.83 ± 10.28	132.5 ± 50.8	53.8 ± 62.9	128.6 ± 34.2	148.8 ± 24.7	6.77 ± 1.96	0.95 ± 0.15	-	61.1	0.65 ± 0.23	-	17.33 ± 7.88
55 ± 12	144 ± 82	-	-	-	7.6 ± 4.2	1.16 ± 0.11	2.8 ± 0.6	100% of subclinical hypothyroid patients were antibody positive	0.66 ± 0.16	-	-
65.7 ± 19.3	Median 106.3 (range 44.3 – 327.7)	-	104.4 ± 33.8	152 ± 30	Median 5.3 (range 3.7–15.8)	1.06 ± 0.16	0.31 ± 0.04	51	-	-	4.8 ± 3.2
52 ± 14	138 ± 82	-	-	-	10.9 ± 5.8	1.15 ± 0.11	2.7 ± 0.4	100	-	-	9.2% ± 4.8%, p = 0.1
49 ± 9	155 ± 84				10.5 ± 6.6	1.17 ± 0.1	2.7 ± 0.4				14.0% ± 4.5%, P < 0.01
50.4 ± 7.8	132 ± 83				11.0 ± 7.5	1.16 ± 0.1	2.9 ± 0.6				No change
54.7 ± 7.4	88.1 ± 30.0	10.7 (range 9.0–65.0)	98 ± 24	152 ± 38	Mean: 1.32 (range: 0.34–2.59)	1.08 ± 0.24	3.2 ± 0.5	-	0.67 ± 0.13	0.85 ± 0.32	-
57.8 ± 11.6	102.7 ± 53.1	15.5 (range 9.0–160.0)	118 ± 49	169 ± 29	Mean: 6.01 (range: 3.67–14.5)	0.84 ± 0.19	3.0 ± 0.6	-	0.77 ± 0.14	0.91 ± 0.18	-

Table 2. Outcomes.

Author/year	Baseline mean IMT (mm)	Follow-up mean IMT (mm)	Baseline maximum IMT (mm)	Follow-up maximum IMT (mm)	Baseline FMD %	Follow-up FMD%
Blum 2018	NA	Levothyroxine:0.85 ± 0.14 Placebo: 0.82 ± 0.13 difference 0.02 95%CI −0.01 to 0.06, p = 0.30	NA	Levothyroxine: 1.10 ± 0.22 Placebo: 1.07 ± 0.18 difference 0.03 95%CI −0.03 to 0.09, p = 0.35	NA	NA
Ersoy 2012	NA	NA	NA	NA	NA	NA
Cabral 2011	Levothyroxine: 0.66(0.11) Observation: 0.65(0.23)	Levothyroxine: 0.66(0.15) Observation: 0,67(0,18)	NA	NA	Levothyroxine: 16.81 (7) Observation: 17.33(7.88)	Levothyroxine: 18.52(7.44) Observation: 13.10(4.75)
Duman [1] 2007	Levothyroxine: 0.65(0.99) Simvastatin: 0.67(0.10)	Levothyroxine: 0.55(0.08) Simvastatin: 0.58(0.08)	NA	NA	NA	NA
Duman [2]2007	NA	NA	NA	NA	Levothyroxine: 20.5(9.0) Simvastatin: 18.2(7.0) Placebo: 20.2(6.2)	Levothyroxine: 19.2(7.5) Simvastatin: 17.4(3.4) Placebo: 18.5(4.8)
Razvi 2007	NA	NA	NA	NA	Levothyroxine: 5.1 (3.3) Placebo: 4.6 (3)	Levothyroxine: 5.9 (3.1) Placebo: 4.2 (3) Adjusted difference: 1.6 (1.2 to 2.1) P < 0.001
Monzani 2004	Levothyroxine: 0.76 (0.14) Placebo: 0.74 (0.13)	Levothyroxine: 0.67 (0.13) Placebo: 0.77 (0.14)	Levothyroxine: 0.95 (0.34) Placebo: 0.89 (0.20)	Levothyroxine: 0.85 (0.32) Placebo: 0.91 (0.18)	NA	NA

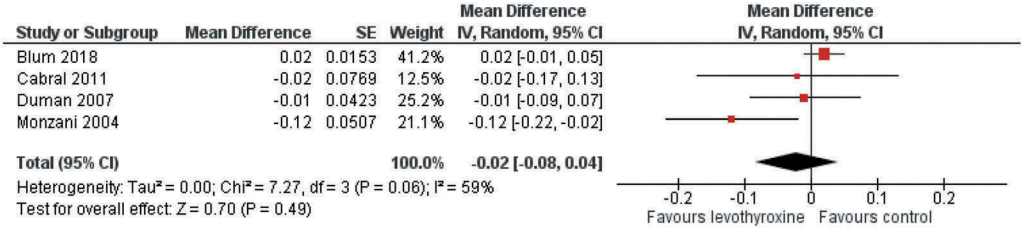

Figure 1. Forest plots of primary outcome.

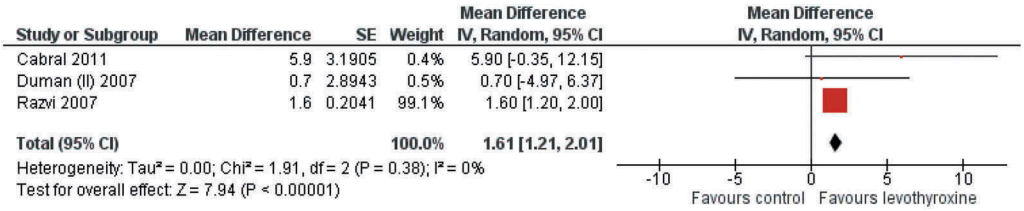

Figure 2. Forest plots of secondary outcome.

treating patients with SCH are highly needed especially among individuals less than 65 years of age.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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