



Subclinical hypothyroidism: to treat or not to treat, that is the question!

A systematic review with meta-analysis on lipid profile

Isabel M Abreu¹, Eva Lau^{1,2,3}, Bernardo de Sousa Pinto¹ and Davide Carvalho^{1,2,3}

¹Faculty of Medicine, University of Porto, Alameda Professor Hernâni Monteiro, Porto, Portugal

²Department of Endocrinology, Diabetes and Metabolism, Centro Hospitalar S. João, Alameda Professor Hernâni Monteiro, Porto, Portugal

³Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Porto, Portugal

Correspondence should be addressed to I M Abreu

Email
isabelmrabreu1992@gmail.com

Abstract

Previous studies suggested that subclinical hypothyroidism has a detrimental effect on cardiovascular risk factors, and that its effective treatment may have a beneficial impact on overall health. The main purpose of this review and meta-analysis was to assess whether subclinical hypothyroidism treatment is of clinical relevance, based on cardiovascular risk parameters correction. A systemic research of the literature using MEDLINE tool was performed to identify the relevant studies. Only placebo-controlled randomized control trials were included. A quantitative analysis was also performed. This systematic review and meta-analysis of randomized placebo-controlled trials assess the different impact of levothyroxine vs placebo treatment. A significant decrease in serum thyroid-stimulating hormone and total and low-density lipoprotein cholesterol was obtained with levothyroxine therapy (66, 9 and 14%, respectively) and, although modest, this could be significant in terms of reduction of the incidence of coronary artery disease. Other significant results of lipid parameters were not obtained. This systematic review provides a strong evidence-based data in favour of specific changes and beneficial effects of levothyroxine treatment.

Key Words

- ▶ subclinical
- ▶ hypothyroidism
- ▶ treatment
- ▶ lipids

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Introduction

Subclinical hypothyroidism (SCH) is diagnosed biochemically when both serum-free thyroxine (FT4) and free triiodothyronine (FT3) are within the normal range, whereas the serum thyroid-stimulating hormone (TSH) is elevated (1). Although considered an asymptomatic disorder, some patients may present non-specific symptoms, which can be suggestive of hypothyroidism (2, 3). The prevalence of SCH in the population is relatively high, and it varies from between 4% and 20%. Furthermore, it depends on gender and age, usually occurring more frequently over the age of 60, with a prevalence of around 15% and 8% for women and men, respectively.

Thyroid dysfunction has significant public health consequences. Overt thyroid disorder has been widely recognized as being a cardiovascular risk factor, as it is associated with dyslipidaemia, insulin resistance, hypertension, inflammation, oxidative stress, endothelial dysfunction, coagulation disorders and, thus, atherosclerosis (4, 5). Recent studies suggest that this may also be true for SCH. In fact, a growing number of studies have associated SCH with an increased number of cardiovascular risk factors, including hypertension (6), weight gain (7), insulin resistance (8), hypercholesterolaemia, dyslipidaemia (9), and coronary and ischaemic heart diseases (10, 11).



As TSH screening has been shown to be cost-effective when applied to increased risk-associated subpopulations, its widespread use in primary clinical care will increase the number of patients diagnosed with SCH (12). However, management of SCH is still controversial, due to uncertainties related to the magnitude of its clinical benefit. On one hand, current guidelines recommend that SCH should be treated in specific conditions, namely: pregnancy, infertility, patients exhibiting associated symptoms or with high risk of progression to overt hypothyroidism (about 5% per year) (13). On the other hand, some clinicians recommend that most patients with subclinical hypothyroidism should be treated, including those with a serum TSH value below 10IU/L (14).

To our knowledge, the data regarding the effect of levothyroxine treatment on lipid levels in selected patients, including apolipoproteins, originated from small studies with heterogeneous and controversial results. The aim of this study is to establish a relationship between lipid profile and levothyroxine treatment, and also to correlate the results of several studies regarding the impact of SCH treatment on overall cardiovascular risk.

Materials and methods

Search strategy

For the systematic review, a comprehensive search of the Medline database was performed up to September 8th, 2015, using the following query: (thyroid* or hypothyroid*) and subclinic* and (cardiovascular* or cardiac* or dyslipidem*) and (treat* or manage* or levothyroxine). We followed the PRISMA checklist for meta-analysis. The search was restricted to the English language, human species and randomized control trials. Potentially studies eligible for further review were selected by screening their abstracts and title. If a study was considered relevant, then the full-text version was reviewed for further assessment. The references from these papers were used to find articles missing in the initial MEDLINE search. All full-text articles were retrieved. We excluded non-original articles, narratives and systematic reviews, or studies that did not report the outcomes proposed.

Eligibility criteria

To be included in the systematic review, studies had to be randomized placebo-controlled trials of thyroid hormone replacement in adults with subclinical

hypothyroidism. The studies included in the analysis and their characteristics are listed in Tables 1 and 2.

To be included in the meta-analysis, the studies should meet the following criteria: (1) all studies had to be randomized controlled trials comparing levothyroxine with placebo; (2) SCH had to be defined as TSH ≥ 3.5 IU/L with FT4 and FT3 concentrations within the normal reference range; (3) patients must have proved stable elevated TSH levels for at least six weeks before beginning levothyroxine or placebo treatment; (4) the study must have had a prospective evaluation of the effect of levothyroxine or placebo therapy; (5) at least two measures should have been obtained: at least a basal measurement before beginning levothyroxine or placebo treatment, and one after it; (6) the minimal duration of levothyroxine/placebo treatment had to be eight weeks (the minimal period required for an effective levothyroxine treatment); (7) both genders could be included; (8) age had to be ≥ 18 years, as the aim was to evaluate the adult population. The studies must have studied at least one of the outcomes of interest: lipid parameters such as cholesterol, triglycerides and apolipoproteins. Studies with patients who had any disease that could interfere with lipid or cardiovascular measures, hypothalamic/pituitary or other non-thyroid diseases were excluded. We also excluded studies with patients taking thyroid or other medications that could interfere with lipid, cardiovascular or thyroid measurements. The inclusion criteria are detailed in Table 2. It is important to notice that, although Monzani and coworkers (15) fulfilled all the inclusion criteria for the meta-analysis, they studied the impact of SCH treatment on cardiac parameters and not on lipid profile and, therefore, were also excluded from the meta-analysis.

Data extraction

Data from selected studies were extracted to a Microsoft Excel database for further statistical analysis. The outcomes of interest were the changes between control and levothyroxine treatment groups in serum thyroid hormones (namely TSH, FT4 and FT3) in lipids and lipoprotein concentrations (including total, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol; triglycerides; apolipoprotein A, apolipoprotein B; and lipoprotein(a)) and their variances between baseline and end treatment concentrations. Values were converted to SI units, using the following

Table 1 Overview of 16 studies included in qualitative analysis.

Study	Sample size	Age (years)/mean	Country	TSH criteria for SCH (IU/L)	Time of study (months)	Outcomes	Mean dose of L-T4 replacement (µg/day)
	● Placebo (M/W) ◇ L-T4 (M/W)	● Placebo group ◇ L-T4 group					
Cooper <i>et al.</i> (29)	33 (1/32) ● 16 (1/15) ◇ 17 (0/17)	32–78/54.0 ● 32–71 ◇ 44–78	USA	>3.5	12	TSH; T4; T3; peak TSH; prolactin; peak prolactin; weight; basal metabolic rate; water excretion; TC; TG; PEP/LVET and QK _D interval	71.2
Jaeschke <i>et al.</i> (21)	37 (9/28) ● 19 (3/16) ◇ 18 (6/12)	>55/68.0 ● 68 ± 6.4 ◇ 68 ± 9.4	Canada	>6	6	TSH; tT4; tT3; TBG; TG; TC; LDL; HDL	68.0
Meier <i>et al.</i> (22)	66 (0/66) ● 33 (0/33) ◇ 33 (0/33)	18–75/58.0 ● 57.1 ± 1.9 ◇ 57.1 ± 1.8	Switzerland	>5.0	12	TSH; FT4; T3; TC; LDL; HDL; TC/HDL ratio; TG; ApoA1; ApoB-100; Lp(a)	85.5
Monzani <i>et al.</i> (15)	20 (2/18) ● 10 (1/9) ◇ 10 (1/9)	–/32.6 ● 29.2 ± 9.4 ◇ 34.3 ± 12.3	Italy	>3.6	12	BMI; body surface area; SBP; DBP; MBP; HR; TSH; FT4; FT3; EDD; FS; Sth _d ; PWth _d ; LVM; CO; SVR; PEP; ET; PEP/ET; peak E; peak A; E/A; MAT; MDT; IVRT	65.0
Caraccio <i>et al.</i> (23)*	49 (7/42) ● 24 (–/–) ◇ 25 (–/–)	–/35.0 ● – ◇ –	Italy	>3.6	11	BMI; TSH; FT4; FT3; TC; HDL; LDL; TG; ApoA1; ApoB; Lp(a); TC/HDL; LDL/HDL; LDL/ApoB	67.5
Kong <i>et al.</i> (24)	40 (0/40) ● 17 (0/17) ◇ 23 (0/23)	–/– ● 45 ± 4 ◇ 53 ± 3	UK	5–10	6	BMI; TSH; FT4; FT3; TC; HDL; LDL; TG; ApoA; ApoB; sialic acid; mevalonic acid; % lean body weight; resting energy expenditure	–
Christ-Crain <i>et al.</i> (33)	63 (0/63) ● 32 (0/32) ◇ 31 (0/31)	32–79/58.0 ● – ◇ –	Switzerland	>5.0	12	TSH; FT4; T3; tHcy; CRP; Vit B12; folate; creatinine	–
Monzani <i>et al.</i> (30)*	45 (8/37) ● 22 (–/–) ◇ 23 (–/–)	<55/37.0 ● – ◇ –	Italy	>3.6	10.5	BMI; SBP; DBP; TSH; FT4; FT3; TC; HDL; LDL; TG; ApoA1; ApoB; Lp(a); tHcy; Vit B12; folate; maximal IMT; mean IMT	70.0
Christ-Crain <i>et al.</i> (35)	63 (0/63) ● 32 (0/32) ◇ 31 (0/31)	18–75/58 ● – ◇ –	Switzerland	>5.0	12	TSH; FT4; T3; ProANP; NT-proBNP	–
Iqbal <i>et al.</i> (25)	64 (33/31) ● 32 (17/15) ◇ 32 (16/16)	–/– ● 62.7 ± 12.4 ◇ 62.0 ± 11.9	Norway	3.5–10	12	BMI; TSH; FT4; FT3; TC; HDL; LDL; TG; ApoA1; ApoB	97.1
Razvi <i>et al.</i> (31)	100 (18/82) ● 50 (8/42) ◇ 50 (10/42)	18–80/– ● 54.2 ± 12.1 ◇ 53.5 ± 13.3	UK	>4.0	3	TC; endothelial function (FMD); patient-reported outcomes	–
Teixeira <i>et al.</i> (27)*	26 (–/–) ● 15 (–/–) ◇ 11 (–/–)	–/– ● 46.6 ± 9.8 ◇ 53.8 ± 8.9	Brazil	>4.0	12	BMI; TPO-Ab+; TSH; FT4; TC; HDL; LDL; TG; ApoA1; ApoB	–
Teixeira <i>et al.</i> (28)*	38 (3/35) ● 20 (1/19) ◇ 18 (2/16)	–/– ● 46.6 ± 9.9 ◇ 52.5 ± 10.1	Brazil	>4.0	6	TC; HDL; LDL; TG; ApoA; ApoB	–

(Continued)

Table 1 Continued.

Study	Sample size	Age (years)/mean	Country	TSH criteria for SCH (IU/L)	Time of study (months)	Outcomes	Mean dose of L-T4 replacement (µg/day)
	● Placebo (M/W) ◇ L-T4 (M/W)	● Placebo group ◇ L-T4 group					
Mikhail <i>et al.</i> (26)	120 (2/118) ● 60 (1/59) ◇ 60 (1/59)	15–60/– ● 31.76 ± 9.89 ◇ 32.3 ± 10.2	Kuwait	4–10	13	TSH; TC; HDL; LDL; TG	72.0
Nagasaki <i>et al.</i> (32)*	95 (0/95) ● 47 (0/47) ◇ 48 (0/48)	–/– ● 66.0 ± 3.0 ◇ 64.2 ± 2.59	Japan	>4.0	5	BMI; SBP; DBP; pulse pressure; pulse rate; TSH; FT4; FT3; TC; HDL; LDL; TG; CRP; BaPWV; PET/ET ratio	25.8
Martins <i>et al.</i> (33)	22 (0/22) ● 13 (0/13) ◇ 9 (0/9)	–/– ● 44.4 ± 8.9 ◇ 51.7 ± 10.2	Brazil	4–12	12	Left ventricular systolic and diastolic function	–

Studies with (*) were included in meta-analysis.

ApoA, apolipoprotein A; ApoB, apolipoprotein B; BaPWV, brachial-ankle pulse wave velocity; BMI, body mass index; CO, cardiac output; DBP, diastolic blood pressure; EDD, end-diastolic diameter; ET, ejection time; FMD, brachial artery flow-mediated dilatation, an early marker of atherosclerosis; FS, fractional shortening; FT3, free triiodothyronine; FT4, free thyroxine; HDL, high-density lipoprotein; HR, heart rate; IMT, intima-media thickness; IVRT, isovolumetric relaxation time; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); L-T4, levothyroxine treatment; LVM, left ventricular mass index; M, men; MAT, mitral acceleration time; MBP, mean blood pressure; MDT, mitral deceleration time; NT-proBNP, N-terminal prohormone form of brain natriuretic peptide; Peak A, late transmitral flow velocity; Peak E, early transmitral flow velocity; PEP/LVET, pre-ejection period/left ventricular ejection time; ProANP, prohormone atrial natriuretic peptide; PWthd, diastolic posterior wall thickness; QKD interval, time between the Q wave on the electrocardiogram and the detection of the last Korotkoff sound in the antecubital fossa; SBP, systolic blood pressure; Sthd, diastolic interventricular septum thickness; SVR, systemic vascular resistance; TBG, thyroxine-binding globulin; TC, total cholesterol; TG, triglycerides; tHcy, total homocysteine; TPO-Ab+, positive thyroperoxidase antibodies; TSH, thyroid-stimulating hormone; tT3, total triiodothyronine; tT4, total thyroxine; Vit B12, vitamin B12; W, women.

conversion factors (16, 17): to convert FT4 from ng/mL to pmol/L, values were multiplied by 12.87; to convert FT3 from ng/dL to pmol/L, values were multiplied by 15.4; to convert total, HDL and LDL cholesterol from mg/dL to mmol/L, values were divided by 38.67; to convert triglycerides from mg/dL to mmol/L, values were divided by 88.57; to convert apolipoproteins A and B from mg/dL to g/L, values were multiplied by 0.01; both values of lipoprotein(a) were already in milligrams per decilitre and were not converted.

Other data were also extracted from the selected studies: number of patients included (total, levothyroxine and placebo groups), age and gender distribution, TSH criteria for definition of SCH and treatment dosages. This data is shown on Table 1.

Statistical analysis

The statistical analysis was performed using Review Manager, 5.3 edition. The studies were assumed to be heterogeneous and a random model meta-analysis weighted by the inverse variance was first applied. This model assumes that variability is due to sampling error and also to the variability in the population of effects (18). The experimental group was compared to the control group by using the Raw (unstandardized) mean

and standard deviation differences (using the most appropriate formula, taking into consideration that we are studying a pre-post score between baseline and end treatment values) (19). For continuous outcomes, pooled estimates and their 95% confidence intervals were obtained with the random effects method (20). Heterogeneity of treatment effects was assessed for the included studies, using Cochran's χ^2 test, with $P < 0.10$ representing evidence of heterogeneity. The degree of heterogeneity was measured by the I^2 statistic, with substantial heterogeneity indicated by $I^2 \geq 50\%$ (18). The total weight of each study that contributes to the analysis of each parameter is shown in Table 3.

Results

Literature search

The initial MEDLINE literature search included 366 studies, after applying the filter for human species and English language. Subsequently, 343 studies were excluded for the following reasons: (1) 117 studies were non-original or systematic reviews, (2) 181 studies were excluded by screening title and abstracts, and (3) 45 articles were excluded by adding a new filter (Randomized Controlled Trials). The remaining 23 full-text articles were

Table 2 Revised study inclusion criteria.

Study	(1) RCT	(2) SCH definition	(3) Proved SCH	(4) Prospective	(5) Two outcomes	(6) 8 weeks treatment	(7) Adults	(8) Without previous disease	(9) Without previous medication
Cooper <i>et al.</i> (29)	●	●		●	●	●	●		
Jaeschke <i>et al.</i> (21)	●	●		●	●	●	●		
Meier <i>et al.</i> (22)	●	●		●	●	●	●	●	●
Monzani <i>et al.</i> (15)	●	●	●	●	●	●	●	●	●
Caraccio <i>et al.</i> (23)*	●	●	●	●	●	●	●	●	●
Kong <i>et al.</i> (24)	●	●	●	●	●	●	●	●	●
Christ-Crain <i>et al.</i> (33)	●	●		●	●	●	●	●	●
Monzani <i>et al.</i> (30)*	●	●	●	●	●	●	●	●	●
Christ-Crain <i>et al.</i> (35)	●	●		●	●	●	●	●	●
Iqbal <i>et al.</i> (25)	●	●		●	●	●	●	●	●
Razvi <i>et al.</i> (30)	●	●	●	●	●	●	●	●	●
Teixeira <i>et al.</i> (26)*	●	●	●	●	●	●	●	●	●
Teixeira <i>et al.</i> (27)*	●	●	●	●	●	●	●	●	●
Mikhail <i>et al.</i> (26)	●	●		●	●	●	●	●	●
Nagasaki <i>et al.</i> (32)*	●	●	●	●	●	●	●	●	●
Martins <i>et al.</i> (32)	●	●	●	●	●	●	●	●	●
Mean (total)	100% (16)	100% (16)	56% (9)	100% (16)	100% (16)	100% (16)	94% (15)	81% (13)	63% (10)

Studies with (●) met criteria. Criteria not declared in a study were considered not done. Studies with (*) were included in the meta-analysis.

Criteria: 1- Randomized placebo-controlled trials; 2- SCH defined as TSH ≥ 3.5 IU/L with FT4 and FT3 concentrations within the normal reference range; 3- proved stable elevated TSH levels for at least six weeks before beginning levothyroxine or placebo treatment; 4- study with prospective evaluation; 5- at least two measurements about outcomes obtained; 6- the minimum duration of treatment was 6 weeks; 7- age ≥ 18 years; 8- patients who had any disease that could interfere with lipid or CV measures, hypothalamic/pituitary or other non-thyroid diseases; 9- patients not taking thyroid medication or others that could interfere with lipid, CV or thyroid mean.

accessed for eligibility, and 7 were excluded on account of the lack of outcome of interest. Therefore, the full-text review resulted in 16 eligible studies for qualitative analysis, of which only five studies fulfilled the inclusion criteria described above, and were thus examined in a quantitative manner. The literature search process is summarized in Fig. 1.

Characteristics of the study

Table 1 summarizes the characteristics of the 16 randomized controlled trials included in this analysis, making a total of 867 participants, including both men and women, of whom 436 were randomized to placebo

treatment, and 431 to active treatment. The five studies included in the meta-analysis have a total of 253 patients, of whom 128 and 125 were randomized to receive placebo and levothyroxine treatment, respectively. Only adults were included.

Our systematic review and meta-analysis aims to evaluate the impact of the treatment of mild thyroid dysfunction on the cardiovascular risk profile. All of the 16 studies included were double-blind, randomized placebo-controlled trials, and assessed a variety of cardiovascular risk factors, ranging from lipid profile to echocardiographic parameters, to analyse the effect of levothyroxine treatment. Nine of sixteen studies focused mainly on lipid profile (21, 22, 23, 24, 25, 26, 27, 28),

Table 3 Weight of each study that contributes to the analysis of each parameter (thyroid hormones and lipid parameters).

	Caraccio <i>et al.</i> (23)	Monzani <i>et al.</i> (30)	Teixeira <i>et al.</i> (27)	Teixeira <i>et al.</i> (28)	Nagasaki <i>et al.</i> (32)
TSH (%)	–	–	27.8	37.8	34.4
FT4 (%)	25.0	22.1	16.6	17.4	18.9
FT3 (%)	51.9	33.0	–	–	15.2
Total cholesterol (%)	22.4	20.8	14.3	23.1	19.5
LDL cholesterol (%)	24.9	26.1	11.4	19.6	18.1
HDL cholesterol (%)	24.4	25.2	10.7	17.3	22.4
Triglycerides (%)	19.9	32.3	10.1	22.4	15.3
Apolipoprotein A (%)	24.7	22.5	23.0	29.8	–
Apolipoprotein B (%)	21.1	9.1	31.6	38.3	–

Table 4 Mean percentage change between pre and post treatment values for each study for thyroid hormones and lipid parameters.

	TSH			Free thyroxine (FT4)			Free triiodothyronine (FT3)		
	Before	Change	% Change	Before	Change	% Change	Before	Change	% Change
<i>Caraccio et al. (23)</i>									
T4	–	–	–	11.6	2.8	24	4.8	0.3	6
Placebo	–	–	–	12.7	0.2	2	4.8	0.1	2
<i>Monzani et al. (30)</i>									
T4	–	–	–	11.3	2.6	23	4.8	0.1	2
Placebo	–	–	–	10.9	–0.1	–1	4.6	0	0
<i>Teixeira et al. (27)</i>									
T4	8.0	–5.88	–74	12.9	4.1	32	–	–	–
Placebo	8.4	–3.5	–42	12.9	2	16	–	–	–
<i>Teixeira et al. (28)</i>									
T4	7.5	–4.6	–61	14.2	0	0	–	–	–
Placebo	8.01	–2.01	–25	14.2	1.2	8	–	–	–
<i>Nagasaki et al. (32)</i>									
T4	7.32	–4.62	–63	14.5	1.5	10	5.06	0.08	2
Placebo	7.25	–0.24	–3	14	0.8	6	4.92	0.2	4
	Total cholesterol			LDL cholesterol			HDL cholesterol		
	Before	Change	% Change	Before	Change	% Change	Before	Change	% Change
<i>Caraccio et al. (23)</i>									
T4	5.5	–0.5	–9	3.6	–0.5	–14	1.5	–0.1	–7
Placebo	5.3	0	0	3.3	0.1	3	1.5	0	0
<i>Monzani et al. (30)</i>									
T4	5.54	–0.58	–10	3.59	–0.51	–14	1.46	–0.05	–3
Placebo	5.51	0.17	3	3.55	0.1	3	1.47	0.02	1
<i>Teixeira et al. (27)</i>									
T4	5.62	–0.52	–9	3.57	–0.51	–14	1.36	0.06	4
Placebo	4.83	0.41	8	2.94	0.41	14	1.43	–0.18	–13
<i>Teixeira et al. (28)</i>									
T4	5.54	–0.58	–10	3.57	–0.48	–13	1.44	–0.08	–6
Placebo	4.87	0.19	4	3.05	0.38	12	1.43	–0.14	–10
<i>Nagasaki et al. (32)</i>									
T4	5.59	–0.4	–7	3.58	–0.44	–12	1.41	0	0
Placebo	5.53	–0.2	–4	3.56	–0.2	–6	1.38	0.01	1
	Triglycerides			Apolipoprotein A			Apolipoprotein B		
	Before	Change	% Change	Before	Change	% Change	Before	Change	% Change
<i>Caraccio et al. (23)</i>									
T4	1.3	–0.1	–8	1.618	–0.128	–8	1.096	–0.083	–8
Placebo	1.4	–0.1	–7	1.584	0.031	2	1.053	0.018	2
<i>Monzani et al. (30)</i>									
T4	1.06	–0.07	–7	1.66	–0.14	–8	1.07	–0.09	–8
Placebo	1.07	0.09	8	1.65	0.04	2	1.17	0.01	1
<i>Teixeira et al. (27)</i>									
T4	1.21	–0.02	–2	1.376	0.04	3	0.966	0.059	6
Placebo	1.08	0.31	29	1.338	–0.034	–3	0.915	0.009	1
<i>Teixeira et al. (28)</i>									
T4	1.16	–0.07	–6	1.403	0.093	7	0.948	–0.041	–4
Placebo	1.11	–0.1	–9	1.407	0.019	1	0.889	0.017	2
<i>Nagasaki et al. (32)</i>									
T4	1.34	0.16	12	–	–	–	–	–	–
Placebo	1.37	0.01	1	–	–	–	–	–	–

four focused on both lipid profile and cardiac or vascular parameters (29, 30, 31, 32), two focused essentially on cardiac function and structure (14, 33), one accessed mainly reactive C protein and homocysteine values (34), and another evaluated primarily changes in Pro-A-type and N-terminal pro-B-type natriuretic peptides (35). Two studies also assessed scores to analyse the impact of mild thyroid disease on subjective health and quality of life, and no significant changes were reported (19, 20).

Meta-analysis

Figure 2 shows the overall changes of responses to placebo or levothyroxine treatments in serum thyroid hormones, namely TSH, FT4, FT3, and lipid profile (total, LDL and HDL cholesterol, triglycerides and apolipoproteins A and B). Table 4 shows the mean percentage change between before and post treatment for each variable analysed.

Within the active treatment, TSH values declined by -3.91 IU/L, with a 95% confidence interval (CI)

of -2.62 to -5.20 IU/L, using a random effects model (Fig. 2A). Only three of the five studies considered for the meta-analysis were included in the TSH analysis, as the two studies excluded present data as interval values that could not be compared with the mean and standard deviation of the other three studies. The mean percentage change in serum TSH with levothyroxine treatment was -66% (range of -61% to -74%), compared with a mean percentage change by -23% (range of -3% to -42%) in the placebo group. Serum TSH changes were significantly different, comparing placebo and active group arms ($P < 0.00001$).

During thyroxine-based therapy, an increased in FT4 by 1.59 pmol/L with a 95% confidence interval (CI) of 0.34 – 2.84 pmol/L was noticed (Fig. 2C), using a random effects model. Despite the overall results favouring treatment with levothyroxine, it is possible to observe that three out of five studies crossed the baseline to favour placebo and that there is evidence of heterogeneity of the studies ($P^2 \geq 50\%$ and Cochrane's χ^2 test with $P < 0.10$). Although statistically significant ($P = 0.01$), the studies might be too dissimilar to combine.

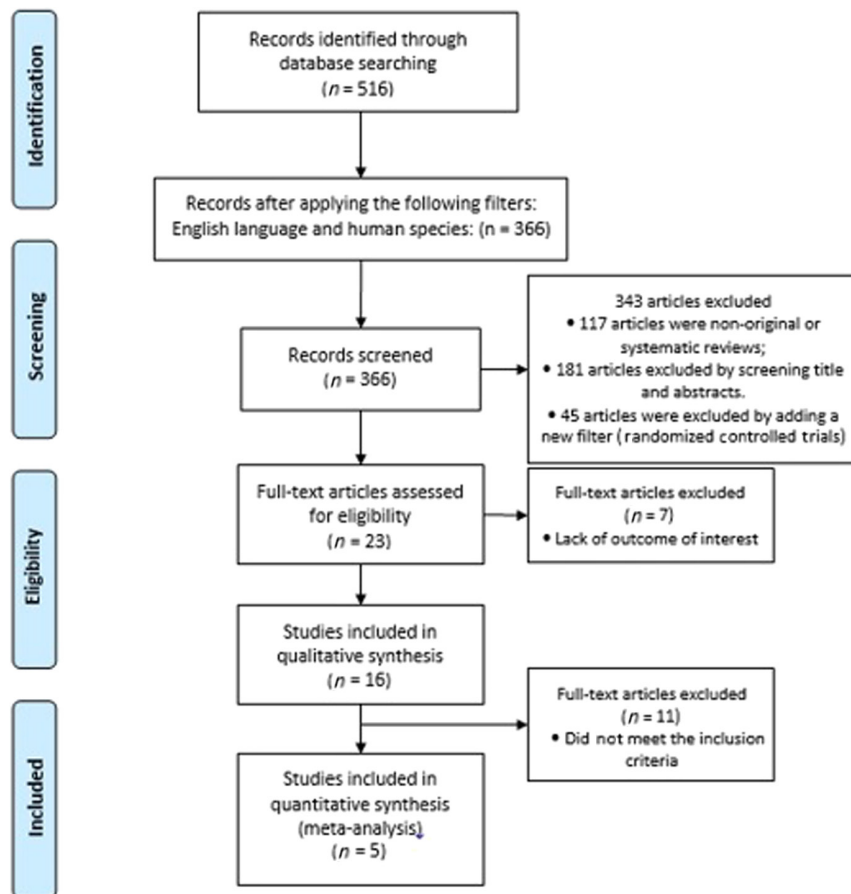


Figure 1
Flow chart of the inclusion criteria for this study.

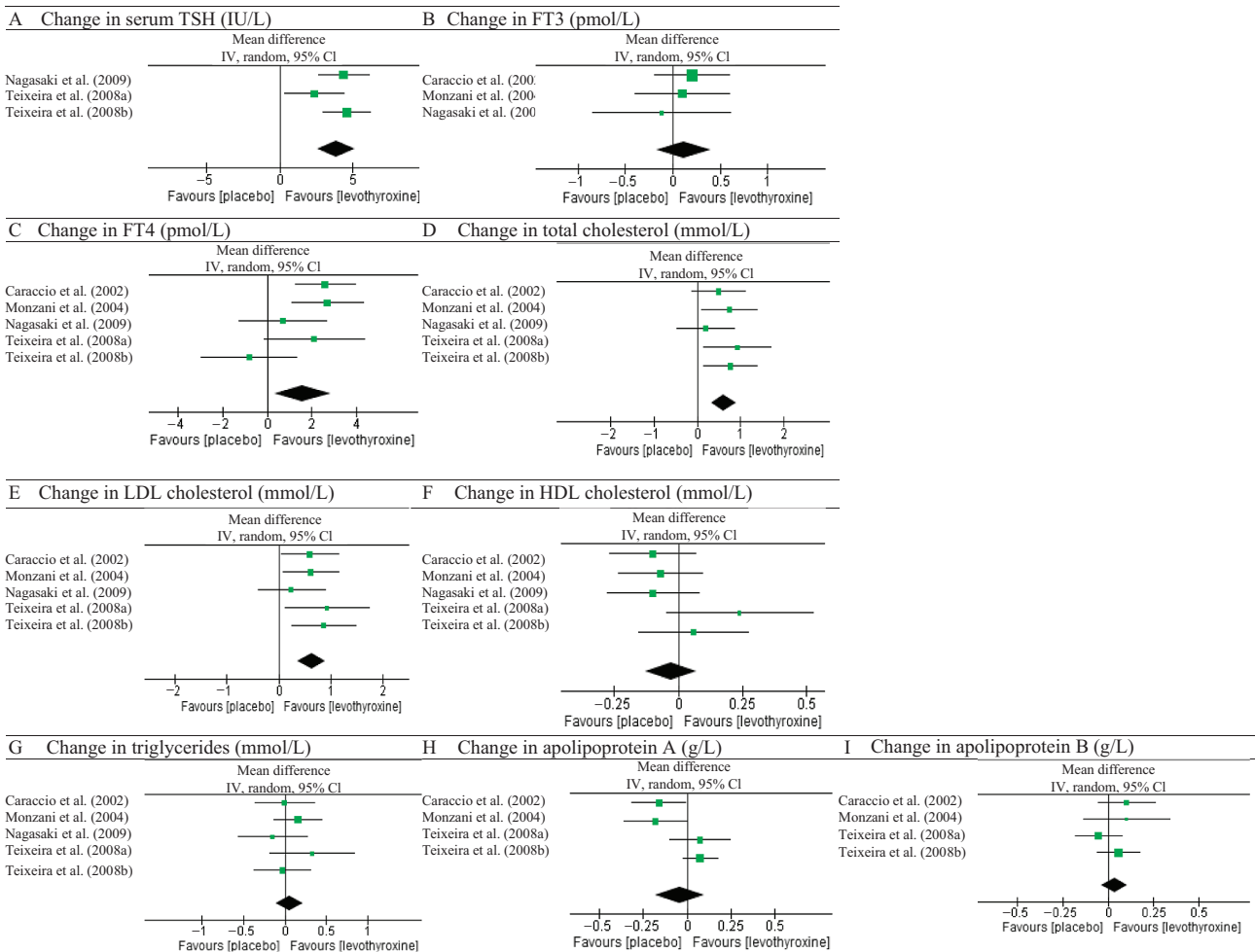


Figure 2

Raw analysis from studies. Changes in thyroid hormones and lipid parameters between levothyroxine and placebo groups.

Finally, only three studies show results regarding FT3 levels, with an increase by 0.12 pmol/L with a 95% IC of -0.17 to 0.40 pmol/L (Fig. 2B). The overall result crossed the baseline and has no significance ($P=0.42$), although it is without heterogeneity.

After initiating the therapy, a reduction in total cholesterol was observed. In random models, serum total cholesterol decreased by -0.62 mmol/L, with a 95% CI of -0.91 to -0.32 mmol/L, equivalent to a mean percentage change of -9% (range from -10% to -7%). The overall effect of levothyroxine treatment showed a significant reduction in total cholesterol levels ($P<0.0001$).

Regarding the LDL cholesterol, a greater decrease by -0.62 mmol/L (with a CI between -0.90 and -0.35 mmol/L) was obtained with levothyroxine treatment than with control. This represented a mean percentage change of -14% (range between -14% and -12%) in serum LDL levels on the levothyroxine group, contrary to the mean

percentage change of 2% (range from -4% to 8%) in the placebo group. These differences between the two groups were significant ($P<0.00001$).

Levothyroxine treatment showed no significant improvement of HDL when compared with placebo ($P=0.59$), with a mean difference of -0.03 mmol/L (ranging from -0.13 to 0.07 mmol/L), using a random effects model.

Using a random effects model, no significant difference of serum triglycerides between the levothyroxine and placebo group was found ($P=0.51$). The mean difference was -0.06 mmol/L, with a 95% CI from -0.22 to 0.11 mmol/L (for heterogeneity $I^2=0\%$).

Only four out of five studies analysed the effect of levothyroxine on serum apolipoproteins A and B. No significant overall effect was found for both ($P=0.57$ for apolipoprotein A, and $P=0.41$ for apolipoprotein B between levothyroxine and placebo treatments). Notably, significant heterogeneity was found regarding

apolipoprotein A (χ^2 test with $P=0.01$ and $I^2=73\%$), and thus the studies might be too different to support a conclusion. An overall decrease of serum apolipoprotein A by -0.04g/L (95% CI from -0.18 to 0.10g/L) and of apolipoprotein B by -0.04g/L (95% CI from -0.11 to 0.03g/L , with heterogeneity χ^2 test of $P=0.41$ and $I^2=0\%$) between the two groups was shown.

Discussion

Subclinical hypothyroidism is progressively being associated with increased cardiovascular risk and poor outcomes, such as atherosclerosis and the associated cardiovascular events. This systematic review and meta-analysis of randomized placebo-controlled trials assesses the different impact of levothyroxine vs placebo treatment. We assessed parameters frequently used on a daily basis, such as lipid profile (including total, LDL and HDL cholesterol, and triglycerides). Moreover, additional selection criteria were chosen to better reflect a population with normal cardiovascular risk and no previous/current treatments, which could interfere with the analysed parameters. Thus, the main purpose of this review and meta-analysis was to assess whether managing subclinical hypothyroidism is of clinical value, based on lipid profile as cardiovascular risk parameters.

Throughout the meta-analysis we found a statistically significant decrease on total and LDL cholesterol with levothyroxine treatment compared with the placebo group, but not on other lipid parameters. It should be emphasized that decline in total and LDL cholesterol induced by levothyroxine therapy, although modest (9% and 14%), could be significant in terms of the reduction in the incidence of coronary artery disease (36), as LDL cholesterol is strongly associated with increasing rates of atherosclerosis, cardiovascular disease, stroke and other vascular complications (37). The Helsinki Heart Study has shown that, in men, a reduction of only 7% in LDL cholesterol levels is associated with a 15% reduction in the incidence of coronary heart disease (38), although comparable data are not available for premenopausal women. Our study showed a decrease in LDL cholesterol twice compared to that reported in Helsinki Heart Study (14% vs 7%), which could be translated to further cardiovascular risk reduction. Helfand and Redfern (39) showed that a 0.6mmol/L reduction in serum total cholesterol levels in a 60-year-old woman, with no other risk factors, would reduce the 10-year risk of ischaemic heart disease from 10% to 9%. Hence, 1000 women would

need to be treated to prevent one new case of ischaemic heart disease per year.

Overall, concerning the changes in lipid profile, two studies showed no changes in serum cholesterol or triglycerides levels within the active levothyroxine treatment group (29, 32). On the contrary, others reported statistically and clinically significant reductions on total and LDL cholesterol within the levothyroxine treatment group (22, 23, 25, 26, 27, 28, 30, 31). These reductions were significant when comparing to the placebo group in some studies (21, 22, 23, 24, 25, 27). While Mikhail and coworkers (26) also obtained a significant decrease in triglycerides levels, Meier and coworkers (22) and Iqbal and coworkers (25) obtained a significant reduction on apolipoprotein B-100 levels within levothyroxine group. Additionally, it was hypothesized that, since the apolipoprotein B-100/LDL cholesterol ratio did not change, levothyroxine treatment resulted in smaller and more atherogenic LDL particles, instead of a depletion of LDL cholesterol (22). Additional sub-analyses were performed in order to study the particularities of levothyroxine treatment. A greater lipid-lowering effect of levothyroxine treatment was found in patients with: elevated pre-treatment total and LDL cholesterol ($\geq 6.2\text{mmol/L}$ and $\geq 4.0\text{mmol/L}$, respectively) and apolipoprotein B levels ($> 1.35\text{g/L}$) (22); serum TSH levels between 0.2 and 2.0 IU/L after 1 year of levothyroxine medication (25), or greater than 8 IU/L after 6 months of levothyroxine treatment (28); and positive antiperoxidase antibodies, body mass index equal to or greater than 25kg/m^2 , and the presence of menopause in women (28).

The analysed studies also showed the impact of subclinical hypothyroidism management on other predictors of cardiovascular events, such as carotid artery intima-media thickness (IMT), brachial artery flow mediated dilation (FMD), brachial-ankle pulse wave velocity (baPWV), C-reactive protein (CRP) and circulating natriuretic peptides levels (atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP)). As a significant reduction of the mean IMT was found when compared to the placebo group (directly related to the decrease of both total cholesterol and TSH), the authors could conclude that not only early carotid artery wall alterations are present in subclinical hypothyroidism, but also lipid infiltration of arterial wall may be the responsible mechanism (30). On the other hand, after three months of treatment, an increase in FMD was observed (31), which could be translated into a reduction in cardiovascular morbidity and mortality (40). BaPWV, a marker of arterial stiffness (41), was found to be significant reduced after 5 months of levothyroxine

treatment, despite the fact that the final values were still higher than euthyroid controls (32). Regarding CRP levels, there is a relative risk factor for cardiovascular diseases when levels are more than 3 mg/L. While some authors did not find significant changes (32), others found that CRP, but not homocysteine values, showed no significant improvement with levothyroxine treatment (34), despite being affected by subclinical hypothyroidism. Thus, they are not determinants to start levothyroxine replacement therapy. Finally, levothyroxine treatment showed no effect on circulating natriuretic peptides levels (35).

Monzani and coworkers (15) and Martins and coworkers (33) focused primarily on cardiac systolic and diastolic function in subclinical hypothyroidism. Both demonstrated that subclinical hypothyroidism is related with overall impairment of both left ventricular diastolic and systolic function, which can be fully reversible with levothyroxine treatment, although it may require a longer period of treatment. Other authors found no changes in myocardial contractility (assessed by the pulse wave arrival time (QK_p interval) or the ratio between the pre-ejection period with left ventricular ejection time (PEP/LVET)) on a group of 33 participants with subclinical hypothyroidism among other medical problems, such as hypertension, angina and diabetes, or/and had previous thyroid treatment (29). However, in a subgroup of patients with the highest PEP/LVET ratio, a significant change occurred on the levothyroxine group (29).

Among sixteen studies, positive correlations, most likely causal, were found between serum TSH and total and LDL cholesterol levels (23, 25, 30). This suggests that increases in total and LDL cholesterol in subclinical hypothyroidism are, to an extent, related to increased TSH levels, and these predict the degree of levothyroxine treatment response. Other positive correlations were found between: serum TSH and total cholesterol, triglycerides and apolipoprotein B levels (27); reduction in total cholesterol levels and increasing FT4 levels (31); diastolic blood pressure, apolipoprotein B to A1 ratio and serum LDL cholesterol (31); homocysteine and FT4 (34); proANP and NT-pro-BNP levels and FT4 (35); IMT and age, LDL cholesterol, triglyceride and apolipoprotein B (30); FMD and FT4 levels (40); and between baPWV and age, baseline pulse pressure (41).

Similar systematic studies had also assessed the impact of levothyroxine treatment on subclinical hypothyroidism. Danese *et al.* (42) conducted a literature review and analysis of prospective studies that evaluated the effect of levothyroxine treatment on serum cholesterol levels in

patients with mild thyroid failure, including other studies besides randomized controlled trials. Also unlike our study, they estimate an upper TSH limit of 20 IU/L. With this study, the authors could conclude that there was an important, although modest (4.3%) reduction in total cholesterol levels with levothyroxine treatment. On the other hand, Villar *et al.* (43) searched the Cochrane Library, MEDLINE, EMBASE and LILACS for all randomized controlled trials comparing thyroid hormone replacement with placebo or no treatment in adults with subclinical hypothyroidism, unlike our study that only compares thyroid hormone replacement with placebo. They could also notice that within six studies that assessed serum lipids, there was a trend for reduction in some parameters following levothyroxine replacement, as some echocardiographic parameters improved after levothyroxine replacement therapy, like myocardial relaxation, as indicated by a significant prolongation of the isovolumic relaxation time as well as diastolic dysfunction.

Limitations

This study may have a language bias, as only English-written reports were included. On the other hand, since only placebo-controlled randomized control trials were included, this systematic review provides a stronger evidence-based perspective about specific changes with levothyroxine treatment. However, only a reduced number of participants were included in the meta-analysis, which may mislead significant changes with levothyroxine treatment. Secondly, the population reviewed may have critical dissimilarities. Although only adults were included, the age range was too high (eighteen to over sixty years) and, as the prevalence of subclinical hypothyroidism increases with age as do other cardiovascular risk factors, the results may not be truly associated with subclinical hypothyroidism and its respective treatment. On the other hand, some patients had previous thyroid diseases or interventions that could interfere with the results observed. Others show positive thyroid antibodies, and these, associated with a familiar story as well, could show more impact on the treatment.

Conclusion

Subclinical hypothyroidism is associated with increased cardiovascular risk, and our meta-analysis and systematic

review indicates that SCH could benefit from thyroid hormones replacement, especially regarding total and LDL cholesterol reduction and overall left cardiac function. As the cost-effectiveness of the screening for mild thyroid dysfunction has already shown to be a favourable strategy (12), early treatment could yield improvements in lipid profile, cardiac structure and function, and could prevent progression to overt hypothyroidism.

Recently, some clinical trials have been carried out. Through International Clinical Trials Registry Platforms, we can understand that at least 9 new randomized placebo-controlled trials are underway. An example is the TRUST study, a new research project from five European universities investigating current treatment practices for people who suffer from a mildly underactive thyroid gland. This project is studying the multi-modal effects of thyroid hormone replacement for 3000 untreated older (≥ 65 years old) adults with subclinical hypothyroidism, and is still currently recruiting patients.

We can conclude that subclinical hypothyroidism is a rising topic all over the world. It is being recognized greatly as a potential cardiovascular risk factor that could interfere with overall morbidity and mortality, and early evidence shows improvement with treatment. Therefore, it is essential that new insights be created to guide clinical practice within the overall population.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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