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Effect of L-thyroxine treatment versus a placebo on serum lipid levels in patients with sub-clinical hypothyroidism

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Abstract. Sub-clinical hypothyroidism is a common disease and whether L-thyroxine replacement treatment improves serum lipid levels in affected patients remains controversial. Thus, the aim of the present meta-analysis was to assess the effect of L-thyroxine therapy on serum lipid levels in sub-clinical hyperthyroidism. Relevant randomized controlled trials (RCTs) containing continuous data, published until July 2015 were retrieved from the Cochrane Library, PubMed, Medline, Google Scholar and Embase databases and subjected to meta-analysis using Review Manager software version 5.2 (The Nordic Cochrane Centre, Copenhagen, Denmark). Seven RCTs comprising 319 patients were included. The overall methodological quality of the RCTs was good. Statistical analysis revealed that serum low-density lipoprotein-cholesterol (LDL-C) levels were significantly decreased after L-thyroxine treatment [mean difference (MD): -0.23; 95% confidence interval: -0.44, -0.03; P=0.02], while changes of total cholesterol (TC), triglyceride (TG) and high-density lipoprotein-cholesterol (HDL-C) were not significant (MD: -0.18, P=0.09; MD: -0.02, P=0.78; and MD: -0.06, P=0.14, respectively). In conclusion, the meta-analysis performed in the present study revealed that compared with placebo treatment, L-thyroxine significantly improved serum LDL-C levels in patients with sub-clinical hypothyroidism, while not significantly affecting TC, TG and HDL-C levels.

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Abbreviations: TSH, thyroid-stimulating hormone; TC, total cholesterol; H/LDL-C, high/low-density lipoprotein-cholesterol; RCT, randomized controlled trial; MD, mean difference; CI, confidence interval; TG, triglycerides

Key words: sub-clinical hypothyroidism, L-thyroxine treatment, serum lipid, randomized controlled trials, meta-analysis

Introduction

Sub-clinical hypothyroidism occurs when thyroid-stimulating hormone (TSH) exceeds the upper reference limit, while free thyroxine and free tri-iodothyronine (FT_3) concentrations remain within the normal range. Sub-clinical hypothyroidism occurs in 4-20% of the adult population and is mostly caused by chronic lymphocytic thyroiditis (1). Other factors that cause sub-clinical hypothyroidism include thyroid injury, such as radioactive iodine treatment or external radiation therapy, drugs, such as iodine-containing compounds, lithium carbonate or interferon, and a period of sub-acute, post-partum or painless thyroiditis (2). The prevalence of sub-clinical hypothyroidism increases with age and is higher in females than in males. Sub-clinical hypothyroidism is a type of mild tissue hypothyroidism; however, it is usually progressive, particularly when serum TSH levels are >10 mU/l and when females are older with the presence of anti-thyroid peroxidase antibodies (3). The symptoms of sub-clinical hypothyroidism are not always obvious; however, they are associated with disease severity, duration and individual sensitivity to thyroid hormone deficiency. Anxiety and depression, as well as a decline in cognitive and memory function are characteristic of sub-clinical hypothyroidism.

The cardiovascular system is a major target of thyroid hormone action. Thyroid hormone deficiency increases the risk for cardiovascular disease by increasing systemic vascular resistance and diastolic dysfunction, while reducing systolic function and cardiac preload (3,4). Hyperlipidemia is one of the risk factors for cardiovascular disease. Thus, the reduction of serum lipid levels may decrease the risk of cardiovascular mortality (5,6). The link between hypothyroidism with dyslipidemia is well documented, while data on this association in sub-clinical hypothyroidism remain limited. Various cross-sectional studies have demonstrated the positive association between TSH, and serum total cholesterol (TC) and low-density lipoprotein-cholesterol (LDL-C) in patients with sub-clinical hypothyroidism (7-9). Previous studies have confirmed that L-thyroxine replacement treatment decreases thyroid size, improves symptoms and signs of sub-clinical hypothyroidism, and normalizes the hemodynamic alterations induced by thyroid hormone deficiency (3). However, only a small number of randomized controlled trials (RCTs) have examined the effects of L-thyroxine on

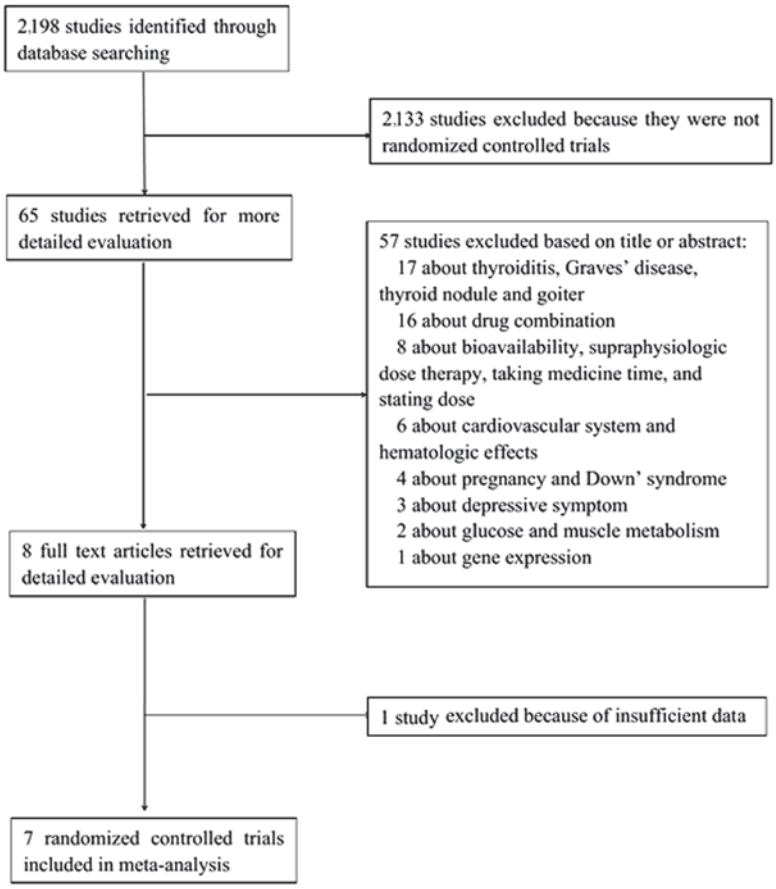

Figure 1. Flowchart diagram for the selection of studies.

serum lipids in patients with sub-clinical hypothyroidism, which has remained controversial due to the inconsistency of the results (10-17). Therefore, the present meta-analysis was performed to elucidate the effect of L-thyroxine replacement treatment on serum lipid levels in patients with sub-clinical hypothyroidism.

Materials and methods

Search strategy. A systematic search of the electronic Cochrane Library (http://www.cochranelibrary.com/), PubMed (https://www.ncbi.nlm.nih.gov/pubmed), Medline (https://www.medline.com/home.jsp), Google Scholar (https://scholar.google.com) and Embase (http://www.embase.com) databases using the search terms 'thyroxine', 'levothyroxin' and 'levothyroxine' was performed (the last search was updated in July 2015). Furthermore, eligible studies were retrieved from the reference lists of the studies identified in order to identify any further studies. The search was limited to studies on humans, but no language limitation was set.

Study selection and data extraction. Data were extracted by two independent investigators, who reviewed all of the studies and cross-checked each others' results to improve accuracy. Only studies that were RCTs comparing the efficacy of L-thyroxine and a placebo treatment on decreasing serum lipid levels in patients with sub-clinical hypothyroidism were included. For each study, data collected included the name of the first author, year of publication, number of patients, the dose of L-thyroxine and placebo used, patient history of thyroid disease, treatment period and serum TSH levels.

Quality assessment. The quality and risk of bias were assessed for each eligible study using Cochrane's risk of bias tool. Bias comprised the following seven areas: Random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases (18,19). The risk of bias for each eligible study was first assessed by two independent investigators and agreement was then reached by consensus. If there was a disagreement, another investigator would estimate the risk of bias for each eligible study.

Statistical analysis. The present meta-analysis was performed using Review Manager software (version 5.2; The Nordic Cochrane Centre, Copenhagen, Denmark). All of the outcomes assessed were continuous data. The majority of the studies included provided baseline, as well as final measurements (6 or 12 months after thyroxine treatment), enabling statistical analysis of differences between data obtained at these two time-points (10,13,15-17). The mean differences were obtained by subtracting the mean levels at baseline from those at the end-point. The standard deviation (SD) of the changes was calculated using the formula according to the Cochrane Handbook for Systematic Reviews of Interventions (20).

Statistical heterogeneity of each study was assessed by visual inspection of forest plots and the extent of inconsistency by I^2 value. A fixed-effects model was used for calculations unless significant heterogeneity existed (I^2>50%), in which case a random-effects model was used (21). P<0.05 was considered to indicate a statistically significant difference.

Results

Selection of studies. The process for the selection of studies for meta-analysis is shown in Fig. 1. The initial literature search yielded 2,198 studies, of which 2,133 were excluded, as they were not RCTs and 57 were excluded based on the title or abstract (were not associated with serum lipids). After full-text scrutiny, one study was excluded due to insufficient data (11), and the seven remaining RCTs that met the inclusion criteria were analyzed (10,12-17). Baseline characteristics of the patients included in the RCTs selected are presented in Table I.

Quality assessment. The quality of the studies was assessed by constructing a risk of bias graph and risk of bias summary (Fig. 2). Each risk of bias item was presented as percentages across all studies included. Fig. 2A shows that the overall methodological quality of the studies was good. High risk of bias was not detected in any of the studies included (Fig. 2B). In five of the studies, the risk of bias was unclear in 1-3 categories, while the two remaining studies met the high-quality criteria.

L-thyroxine improves LDL-C levels in patients with sub-clinical hypothyroidism. In the present study, four separate meta-analyses were performed to assess the effects of L-thyroxine vs. those of a placebo on the levels of TC, LDL-C, triglyceride (TG) and high-density lipoprotein-cholesterol (HDL-C) in patients with sub-clinical hypothyroidism. To assess the effects of L-thyroxine vs. placebo on serum TC levels (mmol/l), all of the seven RCTs were included (10,12-17). No heterogeneity was identified (I^2=42%; P=0.11) and the fixed-effects model was therefore used. The analysis showed no significant differences in the reduction of serum TC levels by either L-thyroxine or the placebo [mean difference (MD): -0.18; 95% confidence interval (CI): -0.40, 0.03; P=0.09] (Fig. 3). Next, the effects of L-thyroxine vs. placebo on serum LDL-C levels were assessed. Six RCTs were included in this analysis and no heterogeneity was found (I^2=34%; P=0.18) (12-17); therefore, the fixed-effects model was used. The analysis showed a significantly higher reduction of serum LDL-C in the patients treated with L-thyroxine compared with that in the placebo group (MD: -0.23; 95% CI: -0.44, -0.03; P=0.02) (Fig. 4). Furthermore, the effects of L-thyroxine vs. placebo on serum TG levels were assessed. Six RCTs were included and no heterogeneity was found (I^2=0%; P=0.92) (10,12-14,16,17); therefore, the fixed-effects model was used. The analysis showed no significant difference between the reduction of TG by L-thyroxine and that in the placebo group (MD: -0.02; 95% CI: -0.17, 0.13; P=0.78) (Fig. 5). Finally, the HDL-C levels were assessed. Six RCTs were included and no heterogeneity was found (I^2=0%; P=0.96) (12-17). Analysis using the fixed-effects model revealed no significant difference

Table I. Characteristics of trials included in the present meta-analysis.

First author, year (Refs.)	Patient no.	Thyroid disease history	Serum TSH levels in L-T4 group (mIU/l)	Serum TSH levels in placebo group (mIU/l)	Initial dose of L-T4 (μg)	Treatment period (weeks)
Cooper *et al*, 1984 (10)	33	Previously treated hyperthyroidism	10.8±2.2	11.1±3.2	50	48
Jaeschke *et al*, 1996 (12)	31	Not mentioned	12.1±6.8	9.4±3.1	25	24
Meier *et al*, 2001 (13)	63	Autoimmune thyroiditis, previously treated Graves's disease and goiter, idiopathic subclinical hypothyroid	14.4±1.7	11.3±1.0	25	48
Kong *et al*, 2002 (14)	27	No history of thyroid disease	8.0±1.5	7.3±1.6	50	24
Razvi *et al*, 2007 (15)[a]	71	Not mentioned	5.4 (3.8-15.8)	5.3 (3.7-13.9)	100	24
Monzani *et al*, 2004 (16)[a]	45	Hashimoto's thyroiditis, previously treated toxic adenoma or multinodular toxic goiter	6.03 (3.65-15.00)	5.68 (3.66-12.60)	25	24
Caraccio *et al*, 2002 (17)[a]	49	Autoimmune thyroiditis, previously treated hyperthyroidism	6.0 (3.70-15.00)	4.90 (3.65-9.00)	25	24

[a]Serum TSH values are expressed as median (range); in all other studies, they are expressed as the mean ± standard deviation. TSH, thyroid stimulating hormone; L-T4, free L-thyroxine.

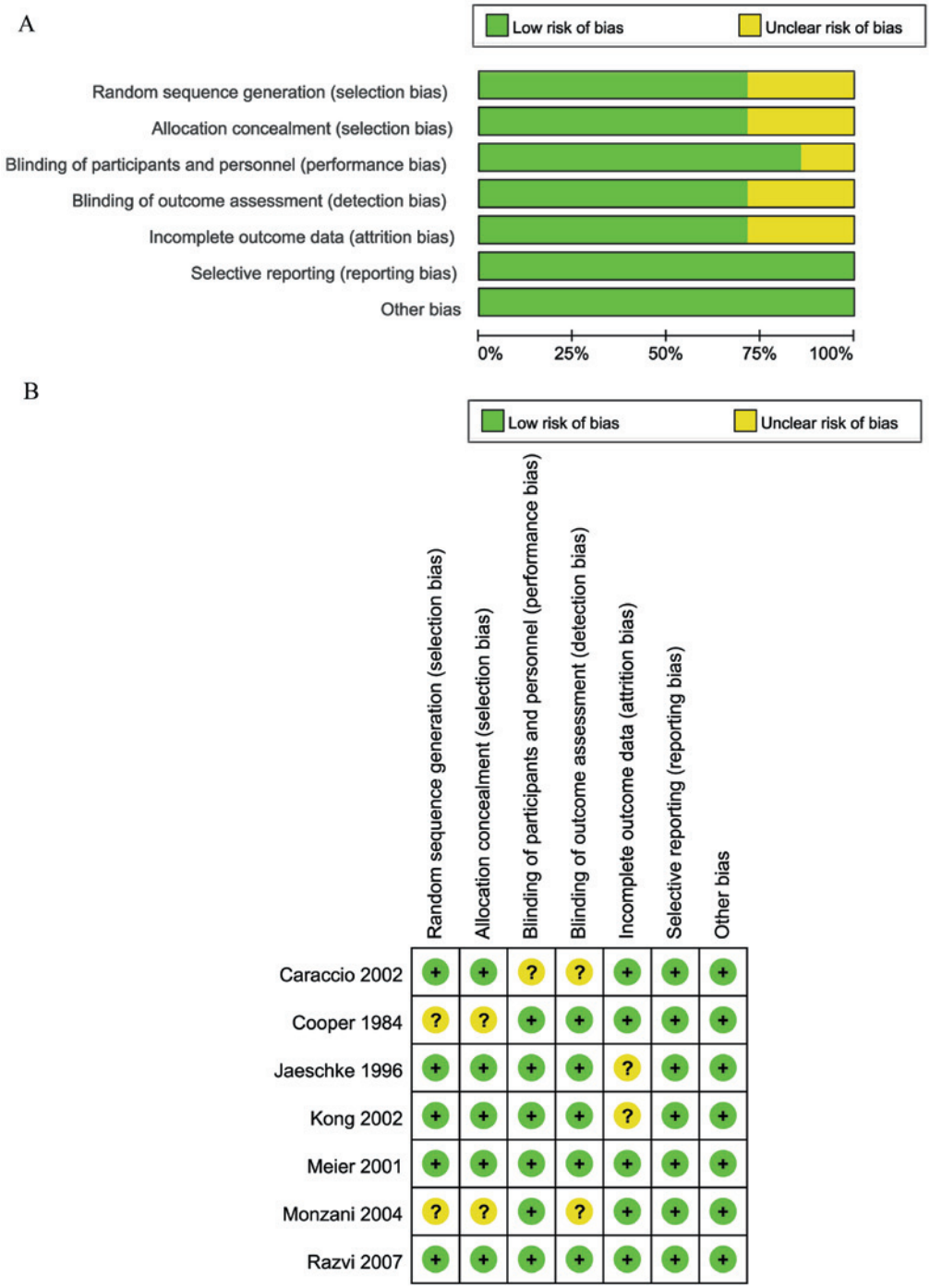

Figure 2. Evaluation of the quality of studies included according to Cochrane. Risk of bias (A) graph and (B) summary.

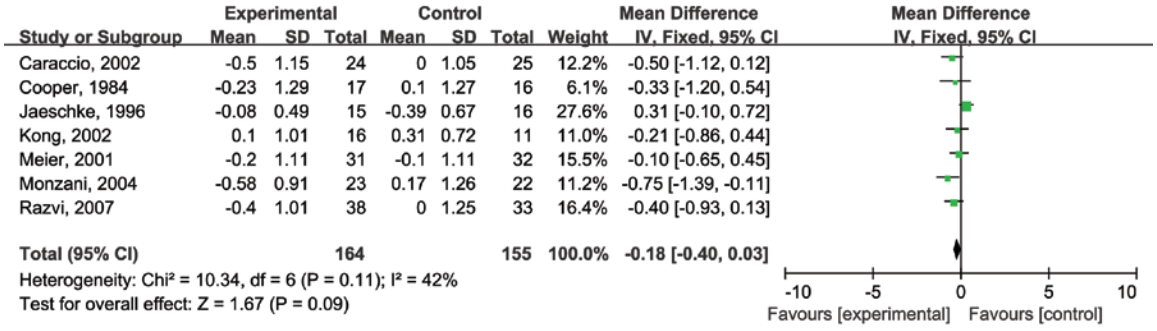

Figure 3. Comparison of the change of serum total cholesterol levels (mmol/l) between patients treated with L-thyroxine (experimental) vs. those treated with placebo (control). SD, standard deviation; CI, confidence interval; df, degrees of freedom; IV, inverse variance.

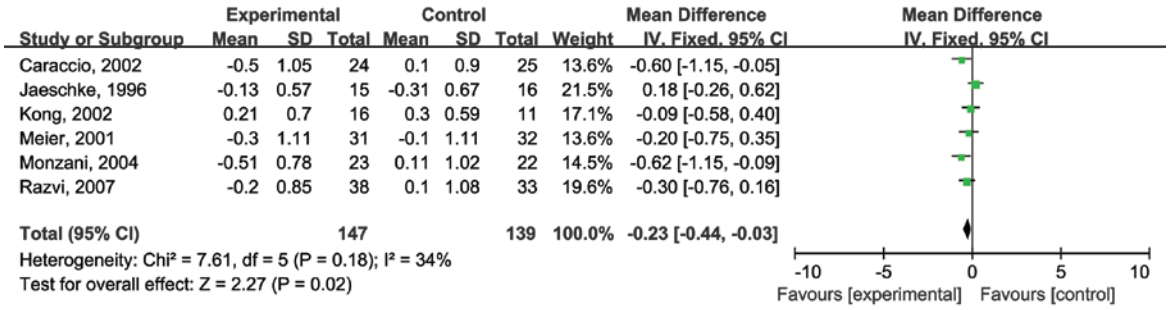

Figure 4. Comparison of the change of serum low-density lipoprotein-cholesterol levels (mmol/l) between patients treated with L-thyroxine (experimental) vs. those treated with placebo (control). SD, standard deviation; CI, confidence interval; df, degrees of freedom; IV, inverse variance.

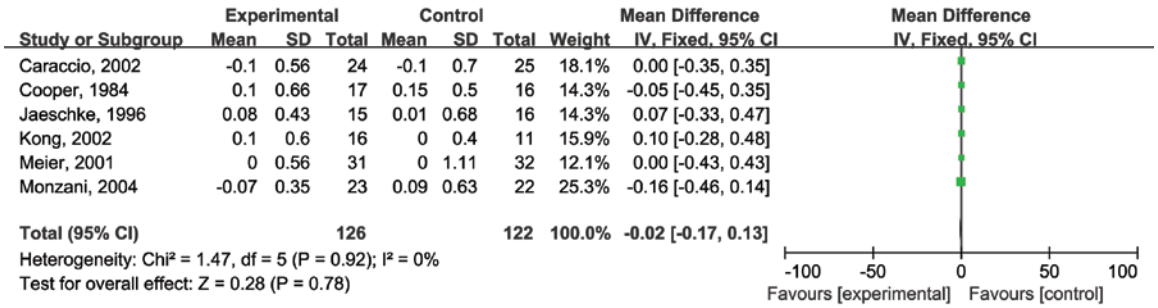

Figure 5. Comparison of the change of serum triglyceride levels (mmol/l) between patients treated with L-thyroxine (experimental) and those treated with placebo (control). SD, standard deviation; CI, confidence interval; df, degrees of freedom; IV, inverse variance.

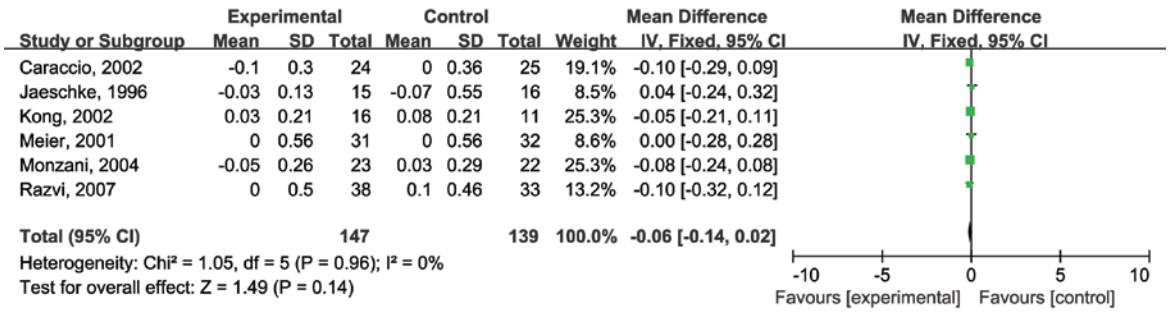

Figure 6. Comparison of the change of high-density lipoprotein-cholesterol levels (mmol/l) between patients treated with L-thyroxine (experimental) and those treated with placebo (control). SD, standard deviation; CI, confidence interval; df, degrees of freedom; IV, inverse variance.

between the L-thyroxine and the placebo group (MD: -0.06; 95% CI: -0.14, 0.02; P=0.14) (Fig. 6).

Discussion

Patients with sub-clinical hypothyroidism, particularly those with positive thyroid antibodies, are at risk of developing overt hypothyroidism at an estimated rate of 2.0-4.3% per year (3,22). L-thyroxine replacement treatment is currently the major therapy for sub-clinical hypothyroidism, which is administered with the following purposes: First, in order to prevent progression to overt hypothyroidism and second, to reduce symptoms of thyroid hormone deficiency (23). Replacement therapy with L-thyroxine reverses systolic and diastolic dysfunction, arterial hypertension, increases in carotid intima-media thickness, endothelial dysfunction and other cardiovascular risk factors (16,24-26). However, the beneficial effect of L-thyroxine replacement on the lipid profiles of patients with sub-clinical hypothyroidism remains controversial (10-17,27,28). Numerous studies have estimated the effect of L-thyroxine replacement treatment on serum lipid levels in patients with sub-clinical hypothyroidism; however, their results were inconsistent. In a recent study by Anagnostis *et al* (22), L-thyroxine replacement treatment exerted no effect on serum lipid levels of patients with mild sub-clinical hypothyroidism, whose TSH levels were <7 mIU/l. However, Tagami *et al* (2) reported a significant decrease of TC and LDL-C following L-thyroxine replacement therapy. A previous quantitative review by Danese *et al* (23) assessed the changes in serum lipoprotein concentrations in patients with mild thyroid failure after treatment with L-thyroxine, revealing that TC and LDL-C levels were reduced subsequent to L-thyroxine treatment, whereas TG concentrations did not change. Danese *et al* (23) also indicated that the serum lipid

levels at baseline and the degree of sub-clinical hypothyroidism were the major factors affecting changes in serum lipid levels. However, a previous meta-analysis by Villar *et al* (29) showed that after thyroid hormone replacement therapy, serum TC, TG, LDL-C and HDL-C levels in patients with sub-clinical hypothyroidism did not significantly improve.

To further clarify the effect of L-thyroxine treatment on serum lipid levels in patients with sub-clinical hypothyroidism, changes in TC, LDL-C, TG and HDL-C levels between baseline and the study end-point were compared with those in patients receiving a placebo and statistically analyzed. The quality of the RCTs included was good and, according to Cochrane, the risk of bias of the studies was limited. Since all of the studies included showed no significant heterogeneity, the fixed-effects model was applied to all analyses. The present study revealed that serum LDL-C levels were significantly decreased following L-thyroxine treatment (P=0.02). However, changes in serum TC, TG and HDL-C levels were not significantly different from those in the placebo group (P=0.09, 0.78 and 0.14, respectively). These results were not consistent with those of the two above-mentioned studies (23,29). The reason for this discrepancy is primarily due to more RCT data being included in the present meta-analysis. The majority of the trials reviewed by Danese *et al* (23) were non-randomized without a control group and a considerable number of the studies had a small sample size, while only two of them were RCTs. Of these, one was included in the present meta-analysis (10), while the other one was excluded due to incomplete data (11). The meta-analysis by Villar *et al* (29) included 12 RCTs to assess the effects of thyroid hormone replacement in patients with sub-clinical hypothyroidism (10-14,16,17,24,30-33). However, the objectives were broad, including reduction of cardiovascular mortality and morbidity, improvement of symptoms, health-associated quality of life, cognitive function, serum lipid levels as well as improvement in TSH and adverse effects, while the present meta-analysis focused on changes in lipid levels alone. The analysis of changes in serum TG, in the present study included all of the RCTs focusing on lipid levels that were included in the meta-analysis by Villar *et al* (29) and an additional RCT (15). For the analysis of LDL-C and HDL-C, the data of three further RCTs were used (15-17). With more data included than in previous studies, the present meta-analysis determined that, compared with placebo treatment, L-thyroxine treatment significantly improvement serum LDL-C levels in patients with sub-clinical hypothyroidism.

There were certain limitations of the present study. First, the limited number of studies and sample sizes included were the major restriction of this meta-analysis (one of the eight articles retrieved was not included in the present meta-analysis due to insufficient data (11) and novel RCTs were scarce). Furthermore, the baseline levels of TSH and serum lipids were not identical among the studies included. The above-mentioned limitations may have engendered bias and affected the quality of this study.

In conclusion, a meta-analysis of complete data from RCTs published until July 2015 on the effect of L-thyroxine treatment on serum lipids in sub-clinical hypothyroidism was performed in the present study. A significant improvement of serum LDL-C was revealed; however, compared with placebo treatment, serum TC, TG and HDL-C levels were not affected by L-thyroxine. High levels of plasma LDL-C levels is associated with occurrence of coronary artery disease; therefore, L-thyroxine may be used to reduce the risk of coronary artery disease. However, further research is required.

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