Systemic Thyroid Hormone Status During Levothyroxine Therapy in Hypothyroidism: A Systematic Review and Meta-Analysis

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Context: The standard of care for overt hypothyroidism is levothyroxine (LT4) at doses that normalize serum TSH levels. Whether this approach universally restores thyroid hormone signaling is unknown.

Objective: To review studies of overt hypothyroidism in which participants received LT4 to normalize serum TSH levels and measure other objective markers of thyroid hormone signaling.

Design: Databases were searched for studies that reported objective markers of thyroid hormone signaling [serum low-density lipoprotein (LDL), total cholesterol (TC), SHBG, creatine kinase and/or ferritin levels; cognition, energy expenditure, and/or renal function] during LT4 monotherapy for overt, primary hypothyroidism among nonpregnant adults with normal serum TSH levels. For studies with LDL, TC, and SHBG outcomes, the data were pooled using random effects meta-analysis.

Results: A total of 99 studies met the inclusion criteria, including 65 reporting serum cholesterol data. The meta-analysis showed that LT4-treated participants with hypothyroidism but normal serum TSH levels had 3.31 $\pm$ 1.64 mg/dL greater serum LDL ($P = 0.044$) and 9.60 $\pm$ 3.55 mg/dL greater serum TC ($P = 0.007$) compared with controls. In studies that had not concomitantly assessed healthy controls, serum LDL was 138.3 $\pm$ 4.6 mg/dL ($P < 0.001$) and serum TC was 209.6 $\pm$ 3.4 mg/dL ($P < 0.001$). A meta-analysis of two studies showed no important differences between the SHBG levels of LT4-treated participants and controls.

Conclusions: In studies of LT4 monotherapy at doses that normalized serum TSH for overt, primary hypothyroidism, not all systemic biological markers of thyroid hormone signaling were normalized, including the serum LDL and TC levels. **(*J Clin Endocrinol Metab* 103: 4533–4542, 2018)**

The healthy thyroid gland produces and secretes both T4 and T3. T4 is considered the prohormone because it has lower affinity for the thyroid hormone receptor, and T3 is the active form of the thyroid hormone. In hypothyroidism, the thyroid gland fails to produce and secrete sufficient thyroid hormone to meet the patient's needs. Hypothyroidism is prevalent, afflicting ~5% of the US population (1). The current standard of care for the treatment of overt hypothyroidism is replacement of thyroid hormone with synthetic T4, called levothyroxine (LT4), at doses that achieve a normal serum TSH level (2). LT4 has been among the most commonly prescribed medications in the United States for >5 years (3). LT4 can be activated to T3 in tissues by enzymes called deiodinases;

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Abbreviations: BMR, basal metabolic rate; CK, creatine kinase; LDL, low-density lipoprotein; LT4, levothyroxine; REE, resting energy expenditure; TC, total cholesterol.

however, the ability of the deiodinases to universally restore thyroid hormone signaling in all tissues has come into question (4) by observations that (i) high serum T4/T3 ratios have been found in patients with hypothyroidism treated with LT4 (5–9); and (ii) a portion of patients with hypothyroidism treated with LT4 have reported that their symptoms have not resolved despite the achievement of normal serum TSH levels (5, 6, 10–12).

Before the development of the serum TSH radioimmunoassay in 1971 (13), other biological markers of thyroid hormone signaling [*e.g.*, clinical examination, basal metabolic rate (BMR)] were used to diagnose hypothyroidism and titrate the doses of thyroid hormone replacement (6). However, these became less popular with the widespread adoption of serum TSH as the most sensitive and specific marker of thyroid status (6). However, the shortcomings of serum TSH have been acknowledged and are not necessarily indicative of universal, peripheral tissue-specific, thyroid hormone status, as would be the ideal marker of "euthyroidism" (2, 14). It is well-established that in hypothyroid rodents, T4 replacement at doses that normalize serum TSH levels does not universally restore other biological markers of thyroid hormone signaling (15–17). The aim of the present systematic review was to evaluate whether objective biological markers of thyroid hormone signaling are universally restored in adults with overt, primary hypothyroidism by LT4 "monotherapy" at doses that normalize serum TSH.

Methods

Data sources and searches

A systematic literature search was performed in adherence with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (18, 19). In January 2016 (updated in October 2017), a medical librarian searched MEDLINE via PubMed 1946 to the present, Scopus 1823 to the present, the Cumulative Index of Nursing and Allied Health Literature (CINAHL Complete) 1937 to the present, ProQuest Dissertations and Theses A&I 1861 to the present, and The Gray Literature Report 1999 to the present.

A combination of subject terms (when available) and keywords were used to locate studies reported from 1970 to October 2017 on LT4 and markers for hypothyroidism, including the BMR, creatine kinase (CK), SHBG, serum total cholesterol (TC), serum low-density lipoprotein (LDL), ferritin, glomerular filtration rate, and cognition (20). When available, database-provided publication type filters were used to exclude letters, comments, and editorials from the results. We also manually searched our personal collections of reports and reports cited by the previously found articles. The full search strategy for PubMed is shown in an online repository (20). RefWorks' and EndNote's deduplication features were used to identify and remove 3133 duplicate records, for a total of 17,905 unique citations (Fig. 1).

Study selection

One author (E.A.M.) reviewed the titles and/or abstracts of the 17,905 studies (Fig. 1). Of these, 17,616 studies were excluded because they were studies of nonpregnant adult humans (defined as age ≥18 years), had only included participants with secondary hypothyroidism, had only included participants with subclinical hypothyroidism, or had not used LT4 to treat the hypothyroid participants (Fig. 1). The studies that treated the participants with hypothyroidism to suppressed serum TSH (defined as less than the reference range specified in that study) or elevated serum TSH (defined as greater than the reference range specified in that study) were excluded. Studies using liothyronine and/or methimazole concurrent with the LT4 intervention were also excluded. In interventional studies measuring ferritin as the outcome measure, those studies that treated their participants with ferrous sulfate in addition to LT4

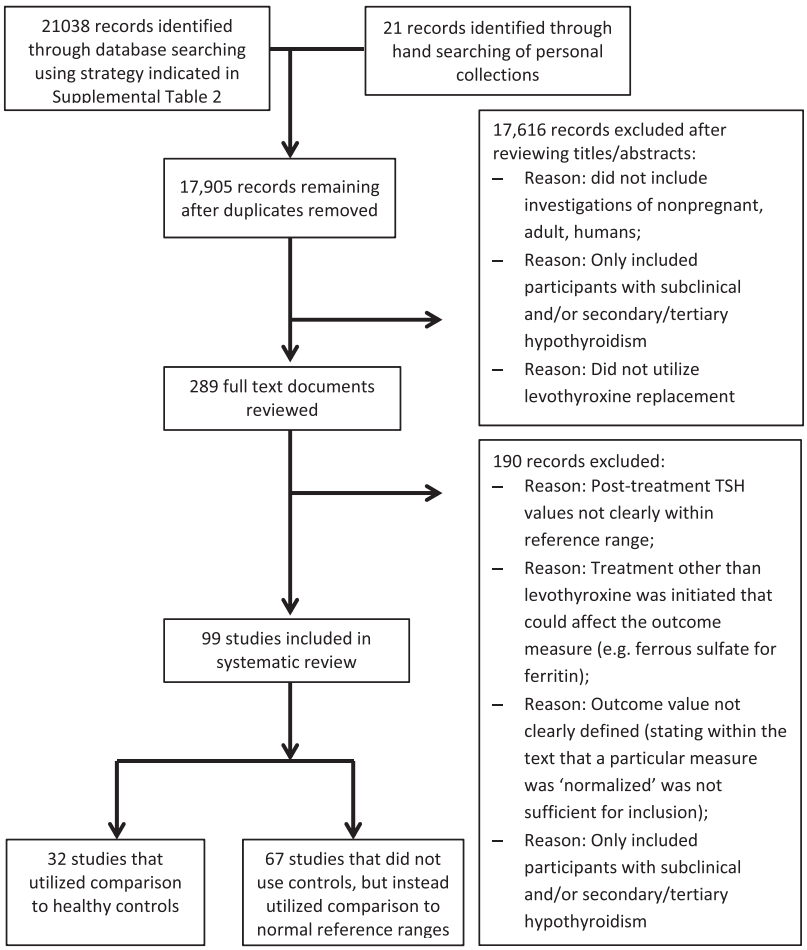

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 flow diagram.

were excluded. If the outcome was renal function, the studies were excluded if they had indicated that participants with baseline chronic renal insufficiency had been included. The outcome data had to have been clearly stated graphically or numerically within the text or as tabular data for the study to be included (*i.e.*, studies stating that a particular outcome had been "normalized" were excluded because our goal was to compile objective measures). When the degree of hypothyroidism had not been specifically indicated (overt vs subclinical), overt hypothyroidism was considered at a TSH value of ≥10 mIU/L. When the degree of hypothyroidism was not specifically indicated (overt vs subclinical) and the baseline TSH was not indicated [*e.g.*, cross-sectional population studies (5, 21)], the study was included.

Thus, 289 full texts were obtained and reviewed, and 190 of these were excluded because they met the exclusion criteria, leaving 99 unique texts, which were included in the present study (Fig. 1). One author (A.C.B.) confirmed that these studies met the inclusion criteria.

Data extraction and quality assessment

The studies were pooled by the outcome measures and the presence of a control group. Data extracted from the studies from both the healthy control groups and LT4-treated participants included sample size, serum TSH levels, TSH reference range, statistically significant differences in serum TSH levels between control and LT4-treated groups, serum level of the outcome measure (*e.g.*, LDL), the outcome measure reference range, statistically significant differences in the outcome measures between the control and LT4-treated groups, and LT4 treatment duration.

Data synthesis and analysis

A pooled treatment effect was estimated for the studies with an intervention and a control group by comparing the change in LDL and TC during the baseline and end-of-study periods. For studies reporting the change in LDL and TC after LT4 treatment, a pooled effect size and 95% CI were estimated. The lipid units were transformed from mg/dL to mmol/L for LDL and TC, as appropriate.

Random-effects meta-analyses for the pooled treatment effect and effect size were conducted using the Hartung-Knapp-Sidik-Jonkman approach. The I^2 statistic was used to test for heterogeneity. All meta-analyses were performed using R software, version 3.4.0 (R Foundation). Publication bias was examined using the Begg rank correlation and Egger regression asymmetry tests.

The meta-analyses were organized by two outcomes and two study designs. The outcomes were change in LDL and change in TC in either a study with no control group or an intervention study with a control group. A meta-analysis was performed, and a pooled estimate and 95% CI was estimated in the four groups. Studies were pooled in each analysis only once.

The presence of a control group, LDL and TC as two outcomes, and a randomized clinical trial or observation study were considered as three potential sources of outcome. This led to three *post hoc* analyses to provide explanations for the observed heterogeneity [i.e., the type of intervention, treatment intervention, and patients enrolled (randomly or observed)]. The test for heterogeneity was statistically significant in the meta-analyses ($P < 0.01$), suggesting that the study effects did not occur over similar conditions with similar patients.

Results

More than 17,000 unique studies were identified in the original search. Most were excluded because they were not studies of nonpregnant, adult participants with overt, primary hypothyroidism receiving LT4 monotherapy at doses that achieved serum TSH levels within the normal range (Fig. 1). A total of 99 texts that met the inclusion criteria were identified by the search, of which 32 studies had assessed LT4 users compared with healthy control participants and 67 had not concomitantly assessed controls.

Cholesterol

Of the 99 included studies, 23 had measured serum cholesterol levels in healthy controls and patients with hypothyroidism treated with LT4 (20). Because overt hypothyroidism is known to elevate both LDL and TC (20), both measures were considered. Most studies (17 of 23) had reported no substantial differences in serum LDL levels between the healthy controls and treated patients. However, one large, cross-sectional population-based study stated that more LT4 users were taking statins (21). In another cross-sectional study, significantly lower LDL levels in the patients with hypothyroidism treated with LT4 were noted compared with the TSH matched-controls; however, these patients were also more likely to be taking statins (5). Most studies (16 of 23) noted no statistically significant differences in the serum TC levels between the healthy controls and treated patients. However, many of these studies had relatively small sample sizes. To better synthesize these data and assess for trends across the studies, we performed a meta-analysis. The meta-analysis showed that LT4-treated hypothyroid participants with normal serum TSH levels had 3.31 ± 1.64 mg/dL greater serum LDL levels (P = 0.044; Fig. 2) and 9.60 ± 3.55 mg/dL greater serum TC levels (P = 0.007) compared with the healthy controls (Fig. 3). We identified studies performed in the era of first-generation TSH radioimmunoassays (20) and then performed another meta-analysis without these studies. The results were similar; the LT4-treated hypothyroid participants with normal serum TSH levels had 3.91 ± 1.73 mg/dL greater serum LDL levels (P = 0.024) (20) and 9.42 ± 3.76 mg/dL greater serum TC levels (P = 0.012) compared with the healthy controls (20).

Of the 99 included studies, 41 had measured serum lipids in patients with LT4-treated hypothyroidism but had not assessed controls (20). Some of these studies had only measured serum TC and had not measured serum LDL. Again, a meta-analysis was used to find important trends in the serum lipids among these studies. The meta-analysis showed that the serum LDL levels in LT4-treated

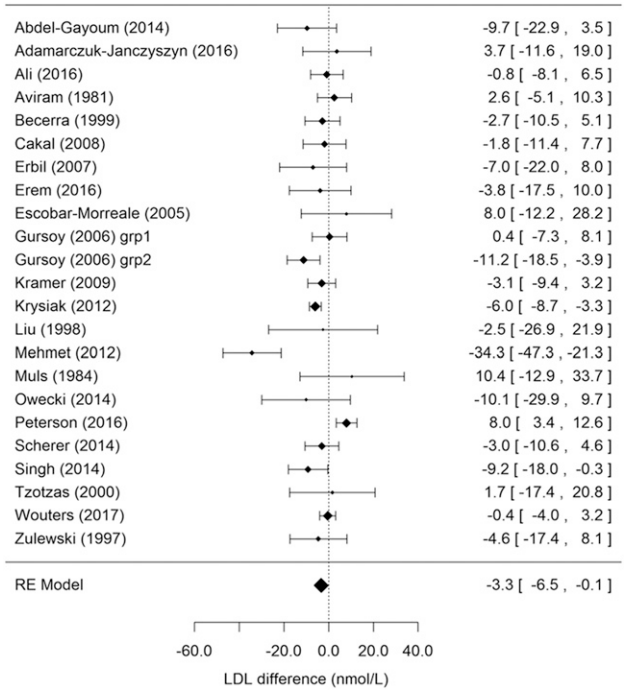

Figure 2. Forest plot of differences in serum LDL levels between healthy controls and LT4-treated participants (5, 21–32, 34–42).

hypothyroidism were 138.2 ± 4.6 mg/dL (95% CI, 129.1 to 147.2; $P < 0.001$; Fig. 4). The meta-analysis showed that the serum TC levels in LT4-treated hypothyroidism were 209.6 ± 3.4 mg/dL (20) [95% CI, 202.9 to 216.2; $P < 0.001$; (20)]. We identified studies performed in the era of first-generation TSH radioimmunoassays (20) and

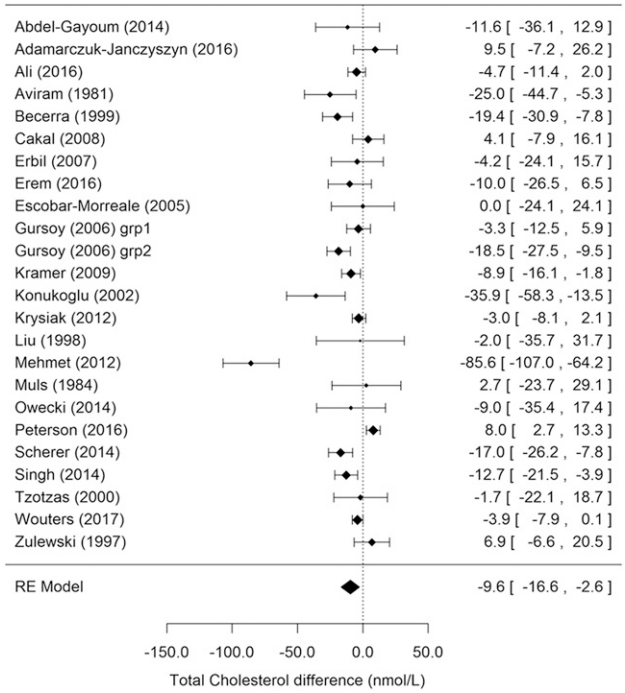

Figure 3. Forest plot of differences in serum TC levels between healthy controls and LT4-treated participants (5, 21–42).

then performed another meta-analysis without these studies. The results were similar; the serum LDL levels in LT4-treated hypothyroidism were 133.4 ± 4.6 mg/dL (95% CI, 124.4 to 142.4; $P < 0.001$ (20), and the serum TC levels were 210.2 ± 3.8 mg/dL (20) (95% CI, 202.7 to 217.7; $P < 0.001$.

SHBG levels

Two studies had assessed SHBG levels in healthy controls and those with LT4-treated hypothyroidism (20). One study of a smaller sample (n = 20) did not identify any difference between the controls and patients treated with LT4 (22). The other, relatively larger, study (n = 114) found that SHBG levels remained statistically significant lower in the LT4-treated individuals ($P < 0.02$), and these participants had been treated for ≥6 months (83). A meta-analysis of the results from these two studies showed that participants with LT4-treated hypothyroidism with normal serum TSH levels had no statistically significant differences (4.1 nmol/L, 95% CI, −15.9 to 24.1; $P = 0.69$) in serum SHBG levels (20).

In the 16 studies that evaluated the SHBG levels in LT4-treated participants but not in healthy controls (20), the reference ranges for the SHBG assays used were only indicated in 7 of the 16 studies. In those seven studies, the mean SHBG levels during LT4 treatment were within the stated reference ranges. A meta-analysis of these was not performed owing to the heterogeneity of the reported reference ranges.

Energy expenditure

Only one study was identified in the search that had compared healthy controls and LT4-treated participants (20) and five studies were identified that had not assessed control subjects, although they measured various energy expenditure-related markers in LT4 users (20). This was unexpected and reflects the abrupt shift in practice standards after the development of the TSH radioimmunoassay, because BMR measurement was commonly used to diagnose hypothyroidism and titrate therapy previously (6). In the single study of 80 patients with LT4-treated hypothyroidism (20), a statistically significant ($P = 0.03$) lower energy expenditure corrected by lean body mass [resting energy expenditure (REE) divided by lean body mass] was found for patients treated with LT4 (28.9 ± 0.3 kcal/kg/day) compared with that of the controls (30.2 ± 0.7 kcal/kg/day) (84).

It is difficult to draw unifying conclusions from the five studies that did not use healthy controls (20) because of the lack of specified reference ranges, differences in the specific variables assessed (REE, REE divided by lean body mass, REE divided by free fat mass, BMR), and

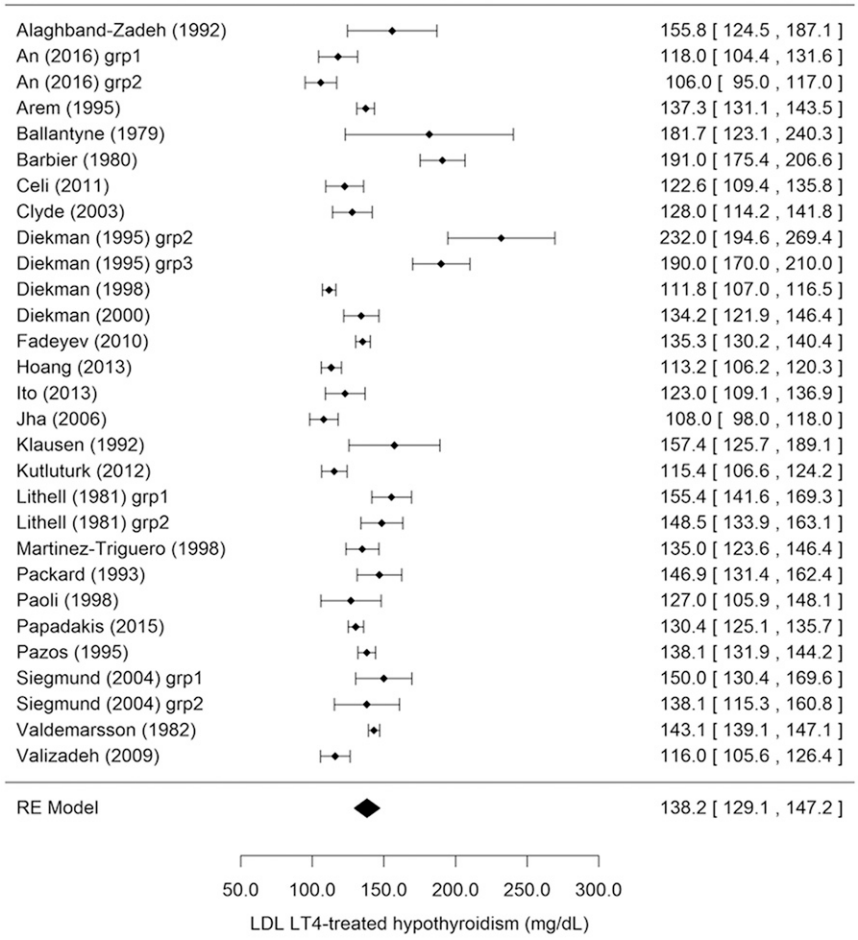

Figure 4. Forest plot of serum LDL levels in patients treated with LT4 with normal serum TSH levels (48–49, 52–54, 56–60, 46–47, 64–68, 70, 74–76, 79–81).

heterogeneity in the study participants in terms of factors known to influence BMR (*e.g.*, age, sex, caloric intake). In the one study that had specified a normal BMR (0%), the patients with LT4-treated hypothyroidism had had their BMRs assessed at varying doses of LT4 (43). In patients with normalized TSH levels (those taking a dose of ≥150 μg of LT4), six of seven patients continued to have a subnormal BMR (20, 43).

Renal function

Six studies that measured markers of renal function in controls and LT4-treated subjects (20) were identified in the search. The markers of renal function included creatinine clearance, estimated glomerular filtration rate, and serum creatinine levels. In five of the six studies comparing controls and LT4-treated participants, no statistically significant were found between the controls and those with LT4-treated hypothyroidism with normal serum TSH levels. The largest study (n = 12,261) (21) did identify significantly lower serum creatinine levels in the LT4-treated individuals (P = 0.001), suggesting normalization of renal function.

Of the 12 studies that did not assess controls concomitant with those with LT4-treated hypothyroidism (20), 4 studies calculated the estimated glomerular filtration rate. The findings for all were consistent with normal renal function. Five studies specified the reference range for serum creatinine, and all five reported mean levels at or less than the reference range. Taken together (20), these studies suggest that markers of renal function are restored by LT4 treatment at doses that normalize the serum TSH.

Creatine kinase

Compared with healthy control subjects, the four studies identified that assessed CK did not show any statistically significant differences, and all values were within the stated reference ranges (20).

In the 14 studies that measured CK but did not concomitantly assess healthy controls, three case reports (85–87) indicated that despite at least 10 weeks of LT4 monotherapy, the participants did not achieve CK levels within the reference range (20). Of the studies identified in the search, the one with the largest sample size (n = 184) reported a reference range for CK of 38 to 174 IU/L and a CK level of 109.7 ± 99.1 IU/L in those with LT4-treated hypothyroidism, suggesting that CK might not have been universally normalized in their participants (44). The interpretation of these results was also challenging owing to the heterogeneity in the reference ranges (20).

Cognition

Seven of the included studies had assessed cognition in healthy controls and patients with LT4-treated hypothyroidism (20). Although different cognitive tests were used in these individual studies, only one study identified any cognitive test results to be worse among the patients with LT4-treated hypothyroidism compared with the healthy controls. That study found that the visual scanning test required substantially longer to complete by the patients with treated hypothyroidism (22). Overall, our interpretation was that these objective cognitive measures had normalized in those with LT4-treated hypothyroidism at doses that normalize the serum TSH. However, this result was limited by the heterogeneity of cognitive tests used in these individual studies.

Twelve studies that measured cognition in LT4-treated participants but not healthy controls were identified (20). It was difficult to cohesively compare these studies and draw conclusions because of the heterogeneity of the cognitive tests used and the lack of stated reference ranges for these tests in most of the studies. In the studies that had specified reference ranges for the cognitive tests used (45, 88, 89), the outcomes were normalized by LT4 treatment.

Ferritin

Only one study that met inclusion criteria had reported on ferritin (5). That study found no difference in serum ferritin levels in LT4-treated participants compared with sex-, age-, and serum TSH-matched healthy controls (20).

Discussion

This systematic review has provided insight into the clinical trials of LT4 therapy for overt hypothyroidism since the implementation of the serum TSH radioimmunoassay as the reference standard for diagnosing and titrating thyroid hormone replacement (6). Albeit no other treatment approach has been shown to be superior to LT4 monotherapy (2), and no peripheral tissue marker has been identified that is more sensitive and specific than serum TSH, these findings should drive further exploration to assess whether patients treated with LT4 with normal serum TSH levels have normal thyroid hormone signaling within all peripheral tissues. Thus, larger population studies investigating patients with LT4-treated hypothyroidism and healthy, TSH-matched controls are needed.

That LT4 users had significantly greater serum LDL and TC levels than healthy controls in the meta-analyses suggests that thyroid hormone-dependent lipid homeostasis was not restored. This is consistent with data from thyroidectomized rats receiving T4 replacement (15). Because two studies contributing large sample sizes (5, 21) noted more LT4 users to be concomitantly taking statins, it is conceivable that the incomplete normalization of LDL and TC was underestimated in the present analysis. In contrast, because TSH screening is an essential part of the workup for dyslipidemia, a group of subjects with hypothyroidism might have a greater prevalence of underlying lipid disorders (unrelated to the hypothyroidism). Our inability to control for statin use in the present study also was a potential confounder. Further studies using TSH-, other medication- (*e.g.*, statin), age-, body mass index-, and sex-matched controls are justified. In addition, in the studies without control subjects, the LDL remained >130 mg/dL and the TC >200 mg/dL. Although these results are difficult to interpret in the absence of control data, based on the current guidelines for cholesterol management (90), these patients would meet the criteria for treatment (lifestyle and/or pharmacologic) even without clinical risk factors for cardiovascular disease. In a previous meta-analysis of the effects of LT4 therapy for overt hypothyroidism, cholesterol was reportedly normalized "in nearly all patient groups," although specific data were not reported and interpretation is difficult in the absence of control subjects (91). Our results could be important because the current clinical guidelines for dyslipidemia and hypothyroidism have acknowledged overt hypothyroidism as a cause of secondary dyslipidemia. However, they have failed to recognize the possible inadequacy of the standard of care for treating hypothyroidism-induced dyslipidemia (2, 90).

Although no benefit in terms of cardiovascular event risk reduction has been definitively shown with the treatment of subclinical hypothyroidism (92), this might not extrapolate to the population of patients with overt hypothyroidism treated with LT4. Considering the high prevalence of hypothyroidism (1) and the relative ubiquity of LT4 use (3), these data support the need for further investigation of the epidemiology of cardiovascular events in LT4 users on a population-wide scale to determine the potential clinical significance of this degree of LDL elevation. It has been shown that lowering TC by ~23 mg/dL results in significantly fewer cardiovascular events (93). If our results are replicated, and if this degree of elevation in serum cholesterol levels is found to be clinically important, this might support the need for amendment of hypothyroidism (2) and lipid (90) guidelines to address screening of serum lipid profiles and treatment thresholds among patients treated with LT4 with overt hypothyroidism.

Such a degree of dyslipidemia could also have implications beyond cardiovascular events, because dyslipidemia has been associated with Alzheimer disease (94). Recently, the Thr92Ala single nucleotide polymorphism (rs225014) in the *DIO2* gene (type 2 deiodinase) has been associated with Alzheimer disease in African Americans (95). It is possible that this polymorphism represents one risk factor and that in the LT4 treatment of hypothyroidism, the resulting degree of residual dyslipidemia would represent another risk factor. If independently confirmed, this would support a personalized medical approach to treating hypothyroid Thr92AlaD2 carriers and more research into the appropriate thresholds for the initiation of cholesterol-lowering drugs for cardiovascular risk reduction and, potentially, as a preventative strategy for neurodegenerative disease.

The LDL and TC results suggest that patients with hypothyroidism treated by LT4 monotherapy at doses

that normalize the serum TSH might have residual hepatic hypothyroidism. However, this was not supported by our SHBG results. Human liver tissue expresses the type 1 deiodinase, which activates T4-to-T3 (96). Our SHBG results had limitations, including relatively few studies, small sample sizes in the individual studies, and the heterogeneity of SHBG reference ranges used in the different studies. Further studies are needed to confirm or refute whether hepatic thyroid hormone status remains suboptimal for all hepatic functions in patients treated with LT4 with normal serum TSH levels.

Patients with LT4-treated hypothyroidism with normal serum TSH levels can express concerns that can be considered residual symptoms from hypothyroidism, including poor memory and weight gain (46, 97). We did not include studies of subjective mood questionnaires in the present review; however, our review of objective cognitive studies suggests that in LT4 treatment of hypothyroidism cognition is intact. Limitations were present, including the heterogeneity of the cognitive tests used in these studies. The field would benefit from the determination of which cognitive tests are most sensitive and specific for patients with hypothyroidism. We found compelling evidence that markers of energy expenditure remain different despite normalization of serum TSH during LT4 monotherapy in patients with overt hypothyroidism; however, again, study heterogeneity limited the interpretation of these data.

Another treatment approach for hypothyroidism has been termed "combination" therapy because it used replacement of both T3 and T4 via either desiccated thyroid or LT4 plus oral synthetic T3 (2, 6). In theory, this approach could obviate concerns about increased T4/T3 ratios with LT4 monotherapy (98). In rodent models, it has been shown to restore biological markers of thyroid hormone signaling (15–17). In the available clinical trials of combination therapy in humans, no benefit compared with LT4 monotherapy has been consistently established (2, 98, 99). In at least one randomized controlled trial, a favorable effect on lipid profile was shown with combination therapy compared with LT4 monotherapy (47); however, this was not confirmed in multiple other studies (99). The currently available human studies might have been limited by the short half-life of the oral synthetic T3. Further clinical trials of combination therapy using delivery mechanisms that provide stable serum T3 levels and maintain physiologic serum T4/T3 ratios, with maintenance of serum TSH within the normal range, are justified.

The present study had several limitations. Notable heterogeneity was present in the identified studies in terms of study type and design, LT4 treatment duration, and the outcome measures assessed. These results should be interpreted with caution because the inability to control for statin use, duration of LT4 replacement, and other potentially confounding variables (including genetic background, diet, and other lifestyle measures) could represent sources of bias. It is possible that the retrieval of research was incomplete with the search strategy and terms used; it is possible that the identification of research that met the inclusion criteria was incomplete, given that >17,000 reports were identified in our search and one author extracted the data.

Conclusion

In the present systematic review and meta-analysis, in adults with overt, primary hypothyroidism, serum LDL and TC were not normalized by LT4 monotherapy at doses that normalize the serum TSH. Clinical trials that use healthy TSH-, medication-, age-, sex-, and race-matched controls are justified to determine whether other biological markers of thyroid hormone signaling, such as the BMR and cognition, are normalized, and to determine the clinical significance of this degree of increased serum LDL and TC on cardiovascular risk.

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Author Contributions: E.A.M. conceptualized the study, designed the study, reviewed all the articles identified in the search, drafted the tables, interpreted the data, and drafted and edited the manuscript. K.B.R. performed the meta-analyses, drafted plots, and edited the manuscript. C.H.M. developed the search strategy design, performed the search, and edited the manuscript. A.C.B. reviewed the 99 articles identified in the search, interpreted the data, and edited the manuscript.

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