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Effect of Thyroxine Therapy on Serum Lipoproteins in Patients with Mild Thyroid Failure: A Quantitative Review of the Literature*

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ABSTRACT

The objective of our study was to estimate the expected change in serum lipoprotein concentrations after treatment with T_4 in patients with mild thyroid failure (*i.e.* subclinical hypothyroidism).

Our data sources included MEDLINE, between January 1966 and May 1999, and review of references from relevant articles.

There were 1,786 published studies identified, 461 abstracts reviewed, 74 articles retrieved, 24 articles evaluated against predetermined entry criteria, and 13 studies systematically reviewed and abstracted.

All studies reported serum total cholesterol concentration changes during T_4 treatment, 12 reported triglyceride changes, 10 reported high-density lipoprotein (HDL) cholesterol changes, and 9 reported low-density lipoprotein (LDL) cholesterol changes.

There were 247 patients in 13 studies. The mean decrease in the serum total cholesterol concentration was −0.20 mmol/L (−7.9 mg/dL), with a 95% confidence interval of −0.09 to −0.34. The decline in serum total cholesterol was directly proportional to its baseline concentration. Studies enrolling hypothyroid participants receiving suboptimal T_4 doses reported significantly larger decreases in serum total cholesterol after thyroid-stimulating hormone normalization than studies enrolling previously untreated individuals with mild thyroid failure [−0.44 mmol/L (−17 mg/dL) *vs.* −0.14 mmol/L (−5.6 mg/dL), $P = 0.05$]. The change in serum LDL cholesterol concentration was −0.26 mmol/L (−10 mg/dL), with a 95% confidence interval of −0.12 to −0.41. Serum HDL and triglyceride concentrations showed no change.

These results, although based on fewer than 250 patients, suggest that T_4 therapy in individuals with mild thyroid failure lowers mean serum total and LDL cholesterol concentrations. The reduction in serum total cholesterol may be larger in individuals with higher pretreatment cholesterol levels and in hypothyroid individuals taking suboptimal T_4 doses. There do not seem to be significant effects of T_4 on serum HDL or triglyceride concentrations. (*J Clin Endocrinol Metab* **85:** 2993–3001, 2000)

THE MILDEST degree of thyroid gland failure is defined by an elevated serum thyroid-stimulating hormone (TSH) concentration in the presence of a normal serum free T_4 concentration (often referred to as "subclinical hypothyroidism"). In general, the prevalence of this condition in women ranges from 4% at age 20 to 17% at age 65 and in men from 2% at age 20 to 7% at age 65 (1–5). Whereas the condition is relatively common, whether one should treat such individuals remains controversial.

Treatment with T_4 sodium is often initiated for two reasons. First, therapy may prevent progression to the symptomatic stage of overt hypothyroidism, which otherwise occurs at a rate of about 5% per year in those with mild thyroid failure (6–10). Second, therapy may also reduce symptoms of thyroid hormone deficiency that have been shown to be present and reversible in about 25% of individuals with mild thyroid failure (11–14). However, it has been less clear whether a relationship exists between mild thyroid failure and serum total, low-density lipoprotein (LDL), or high-density lipoprotein (HDL) cholesterol levels.

Despite various assessments of the literature, the relationship between mild thyroid failure and serum lipid levels is still ambiguous (15–18). Part of the difficulty stems from the range of studies and study designs addressing the topic. Some cross-sectional studies suggest that serum cholesterol levels are significantly higher in individuals with mild thyroid failure than in euthyroid individuals (13, 19–22), In other cross-sectional studies, the differences are not statistically significant (23–25). Still, other cross-sectional studies of hypercholesterolemic individuals report higher prevalences of mild or overt thyroid failure than in normocholesterolemic control groups (26–29). Even in prospective studies, some

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authors consider participants to have mild thyroid failure at TSH levels that may be more indicative of overt hypothyroidism than mild thyroid failure (30–32)

Mild thyroid failure may be present for many years before overt hypothyroidism (33). Therefore, because there is a well-established relationship between an elevated serum cholesterol concentration and atherosclerotic vascular disease (34), knowing whether the treatment of mild thyroid failure with T_4 has the potential to improve lipid profiles is important. Hence, the purpose of this review is to systematically evaluate available prospective studies, to estimate the effect of T_4 therapy on serum lipids across the relevant studies, and to explore potential reasons for the variation in conclusions among these studies.

Materials and Methods

Design

We conducted a literature review and analysis of published studies providing measures of the effect of treating mild thyroid failure on serum cholesterol levels. To be included, a study had to meet the following six entry criteria: 1) the study must have been a prospective evaluation of the effect of levothyroxine therapy; 2) the mean pretreatment basal serum TSH concentration must have been above the upper limit of normal for the assay used in the study, but less than 20 mU/L; 3) individual patients with serum TSH levels between the upper limit of normal and 10 mU/L must have been included; 4) relevant lipoprotein data must have been provided for the subset of patients with mild thyroid failure if other patient types were included in the analysis; 5) the study must have included the mean serum TSH concentration both before and after T_4 treatment; and 6) the study must have included the mean serum total cholesterol level with a variance estimate both before and after T_4 treatment.

In the event that a study included data for subsets of patients stratified by TSH levels, data for the group with the lowest TSH concentrations consistent with the definition of mild thyroid failure (usually TSH 5 to 10 mU/L) were used.

Literature search

To identify the relevant published literature, we conducted a comprehensive, text-word MEDLINE search of both thyroid disease and cholesterol between January 1966 and May 1999. The references from these papers were used to find articles missed in the MEDLINE search. We also contacted many of the authors of papers to request data and information about other unidentified studies.

Evaluation of study design

Two reviewers (M.D.D. and N.R.P.) evaluated the studies using a 13-item checklist of factors related to study internal and external validity (Table 1). If an item was not reported it was not considered to have been done. Discrepancies between reviewers were resolved by agreement. A simple score was calculated by assigning one point for each of the 13 items on the checklist. Sub-scores were calculated for factors related to internal and external validity.

Data abstraction

Changes in serum lipoprotein concentrations [total, LDL, and HDL cholesterol; triglycerides; apolipoprotein A; apolipoprotein B; and lipoprotein(a)] and their variances were abstracted from each study. If variances were not available, *P* values were abstracted. In all other cases, baseline and follow-up concentrations and variances were abstracted.

Analyses

The main results were calculated using both fixed and random effects models (35). Serum lipoprotein changes were weighted according to the reciprocal of their squared SE. (The main results were also calculated using the sample size as the weight, and the results were virtually the same.) In the fixed effects analyses, homogeneity was assessed both overall and within subgroups using a χ^2 test. Using weighted ANOVA, the studies were stratified according to individual items on the study design checklist. Weighted linear regression was used to evaluate the relationship between the baseline level of serum cholesterol and the change in serum cholesterol. Publication bias was assessed using common graphical and computational techniques. All statistical analyses and figures were performed using S-PLUS 4.5 (Mathsoft, Inc., Seattle, WA) and Microsoft Corp. Excel 97 (Microsoft Corp., Redmond, WA).

For each study without a control group, change was calculated as the mean difference between the final and pretreatment measurements for study participants. For each study with a control group, change was calculated as the difference between the two group mean differences. Hence, negative numbers reflect a decrease after initiation of therapy.

TABLE 1. Criteria evaluated by reviewers for an internally consistent and generalizable study

Internal validity
1. Use of randomized, controlled trial design
2. Assessment of medications that can affect thyroid hormone levels or T_4 absorption
3. Attempt to standardize or assess dietary changes during the treatment period
4. Attempt to assess weight changes during the treatment period
5. Mean level of TSH after therapy $\leq$2 mU/L
6. Dose of T_4 titrated for each participant individually
7. Treatment period was at least 12 weeks or 3 months
8. Information available about losses to follow-up
External validity/generalizability
1. Participants drawn from a population-based sample
2. Mean age of participants between 40 and 60 yr
3. Men constitute at least 20% of the sample
4. Free T_4 testing used as an entry criterion
5. Mean level of TSH before T_4 therapy $<$12 mU/L

Results

Search results

There were 1,786 studies identified using MEDLINE. Irrelevant articles were eliminated by inspection of the title, if possible (*e.g.* letters to the editor). Three authors reviewed abstracts (M.D.D., N.R.P., and P.W.L.) of the remaining 461 articles. The remaining 66 studies were retrieved, as were 9 additional citations discovered by reviewing references and communicating with investigators. Of the 75 retrieved studies, 44 nontreatment studies and 6 studies of overt hypothyroidism were eliminated. Of the 25 remaining studies of mild thyroid failure, 12 were excluded after examination against the entry criteria (36–47). The remaining 13 studies were used in the analyses (11, 12, 48–58).

Evaluation of study characteristics

No study fulfilled all 13 criteria related to internal and external validity. Tables 2 and 3 show the overall number of criteria fulfilled in each study, ranging from three to eight, with a median of six. Sample sizes ranged from 7–33, with a median of 15. Only three studies were randomized, all with placebo controls. All studies enrolled at least 75% women, with six enrolling only women. Mean ages in the studies ranged from 32–71 yr.

Only one study sampled patients from a population. Two studies enrolled hypothyroid patients who were inadequately treated with T_4. Two studies enrolled individuals

TABLE 2. Overview of 13 studies of levothyroxine therapy on serum lipids

First author	Yr	Design	Sample size	Mean age (yr)	Selection criteria for patients	Initial TSH (mU/L)[a]	Final TSH (mU/L)[a]	Design score (of 13)
Arem (50)	1990	Before-after	13	32	Hypothyroidism	16.6	3.2	4
Arem (51)	1995	Before-after	14	41	Hypothyroidism	9.1	1.8	6
Bell (52)	1985	Before-after	18	42	Hyperthyroidism	17.9	3.2	7
Bogner (48)	1993	Before-after	7	60	Hypercholesterolemia	4.8	0.7	5
Caron (53)	1990	Before-after	29	35	NR	12.0	1.2	5
Cooper (12)	1984	Parallel RCT	33	54	Hyperthyroidism	10.8	2.6	8
Franklyn (54)	1993	Before-after	11	63	Hyperthyroidism	13.8	1.1	3
Jaeschke (57)	1996	Parallel RCT	31	68	NR	12.3	4.6	7
Miura (49)	1994	Before-after	15	47	Mixed, mostly hyperthyroidism	6.0	3.0	5
Nilsson (55)	1976	Before-after	29	54	Hyper- and hypothyroidism	19.0	5.0	3
Nyström (11)	1988	Crossover RCT	17	58	Community-based screening	7.7	1.9	8
Paoli (58)	1998	Before-after	15	32	NR	5.3	0.6	6
Powell (56)	1989	Before-after	15	71	Arterial clinic	9.8	2.9	4
Median	1990	NA	15	54	NA	10.8	2.6	6

Before-after, Uncontrolled, single-group study; RCT, randomized, placebo-controlled trial; NR, not reported; NA, not applicable.
[a] For controlled studies, TSH data reported for T_4-treated group or period.

TABLE 3. Reviewer-assessed study design factors related to internal validity[a]

First author	Internal validity								External validity				
	1	2	3	4	5	6	7	8	1	2	3	4	5
Arem 90 (50)						●	●	●				●	
Arem 95 (51)		●			●		●			●		●	●
Bell (52)		●		●		●	●			●	●	●	
Bogner (48)					●		●	●		●			●
Caron (53)		●	●		●		●					●	
Cooper (12)	●			●		●	●	●		●		●	●
Franklyn (54)					●		●					●	
Jaeschke (57)	●	●				●	●	●			●	●	
Miura (49)			●	●						●	●		●
Nilsson (55)				●		●				●			
Nyström (11)	●				●		●	●	●	●		●	●
Paoli (58)		●		●	●	●						●	●
Powell (56)						●	●	●					●
Mean (total)	23% (3)	38% (5)	15% (2)	38% (5)	46% (6)	54% (7)	77% (10)	46% (6)	8% (1)	54% (7)	23% (3)	69% (9)	54% (7)

[a] Factors not mentioned within a study were considered not done. See Table 1 for definitions of factor numbers.

with either cardiovascular disease or hypercholesterolemia. Three studies did not adequately characterize the selection of participants. The remaining six studies predominately consisted of patients with a history of ablative therapy for hyperthyroidism.

Seven of the studies neither discussed losses to follow-up nor gave sufficient information from which this could be determined. Of the 127 participants in the remaining six studies, 14 were lost to follow-up. Only four of these individuals were reported to have symptoms that were potentially related to T_4 treatment. Others were in the placebo arm of a study (n = 3), reported unrelated reasons for discontinuing (n = 4), or were not characterized (n = 3).

Total cholesterol

Figure 1A and Table 4 show the changes in the mean serum total cholesterol concentration for each study. The serum total cholesterol level declined after initiation of therapy by −0.20 mmol/L with a 95% confidence interval (CI) of −0.09 to −0.34 (−7.9 mg/dL; 95% CI, −3.3 to −13) using a fixed effects model. However, the χ^2 test ($P = 0.05$) suggested that the studies might be too dissimilar to combine. Because of this heterogeneity, a random effects model was also used, which allowed cholesterol changes to vary not only within each of the studies (as reflected by the study SE), but also between different studies. Using this approach, the mean change was not appreciably different, −0.24 mmol/L (95% CI, −0.06 to −0.42).

The median percentage change in the serum total cholesterol concentration was −5% (range, −14% to 5%). The correlation between the change in serum total cholesterol and the change in the logarithm of serum TSH was 0.26 ($P = 0.01$).

LDL cholesterol

Nine of the 13 studies reported serum LDL cholesterol data (Fig. 1B and Table 4). In the fixed effects model, the mean LDL cholesterol reduction was −0.26 mmol/L, with a 95% CI of −0.12 to −0.41 (−10 mg/dL; 95% CI, −4.0 to −16). The results were more heterogeneous than would be expected by chance ($P = 0.02$). However, the reduction was similar using a random effects model, -0.30 mmol/L (95% CI, −0.01 to −0.54) after therapy.

HDL cholesterol

Ten of the 13 studies reported serum HDL cholesterol concentrations (Fig. 1C and Table 4). There was an increase in HDL cholesterol after therapy by 0.08 mmol/L, with a 95%

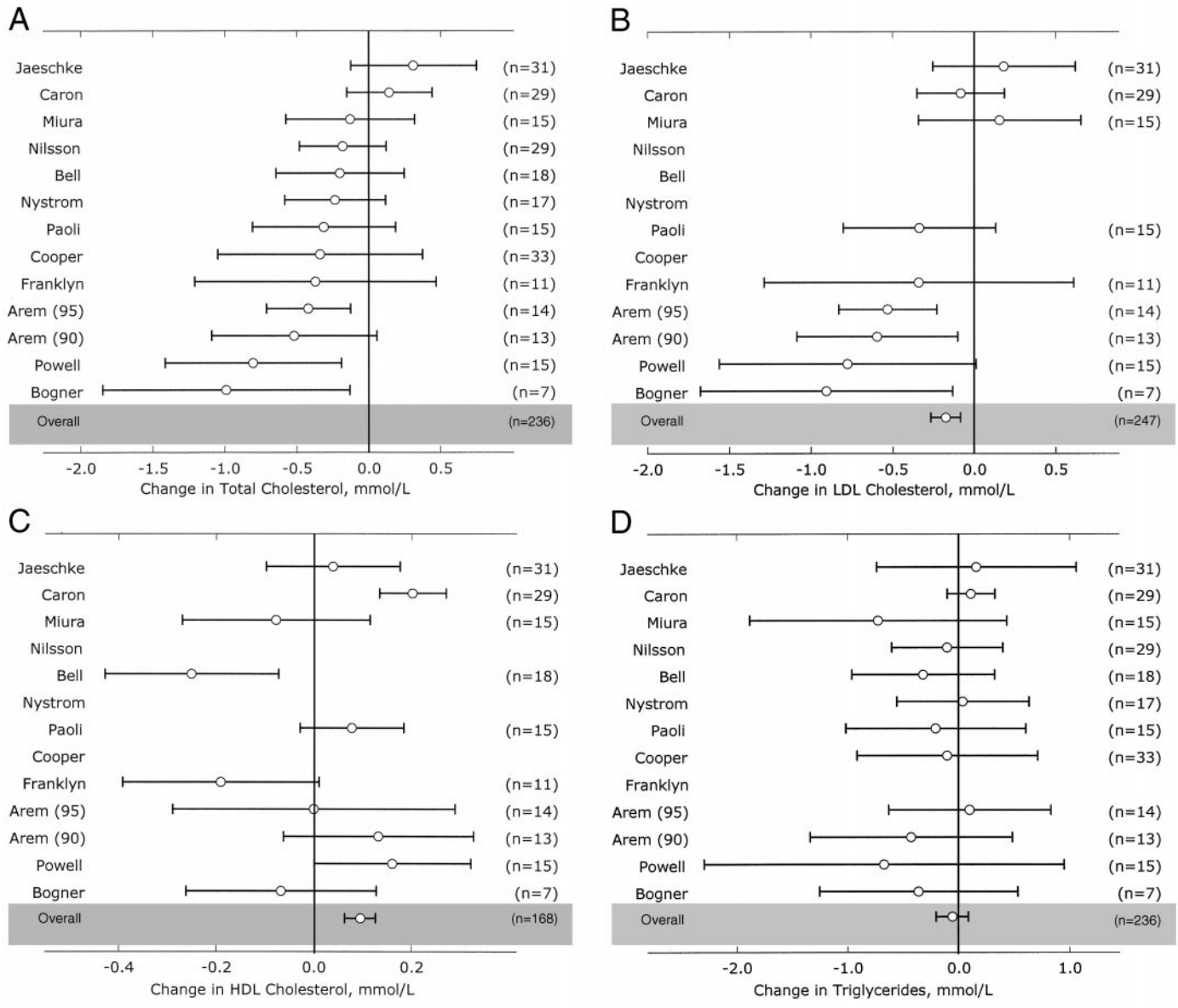

FIG. 1. Changes in serum lipids with T_4 therapy. The mean changes and CIs for total cholesterol (a), LDL cholesterol (b), HDL cholesterol (c), and triglycerides (d) for each study. Studies are ordered by change in total cholesterol, with the overall result across all studies at the *bottom*.

CI of 0.04–0.13 (3.2 mg/dL; 95% CI, 1.6–4.9) in the fixed effects model. Although statistically significant, the increase was driven primarily by one study (53). Again, these results were more heterogeneous than would be expected by chance ($P < 0.001$). However, the results were similar, although nonsignificant, using a random effects approach, 0.02 mmol/L (95% CI, −0.09 to 0.12).

Triglycerides and apolipoproteins

Twelve of the 13 studies reported changes in the serum triglyceride concentration (Fig. 1D). Using a fixed effects model, the mean change was −0.01 (95% CI, −0.08 to 0.06). The test for homogeneity was not rejected, indicating that the results were similar across all of the studies ($P = 0.65$).

Six studies reported changes in the serum apolipoprotein B concentration. The average fixed effects decrease was −8.5 mg/dL (95% CI, −4.2 to −13), and the results were more heterogeneous than would be expected ($P = 0.05$). These same six studies reported changes in serum apolipoprotein A concentration: the average fixed effects increase was 1.1 mg/dL (95% CI, −3.6 to 5.8) and homogeneity was not rejected ($P = 0.27$). Only one study (51) examined the concentration of serum lipoprotein(a) and reported a slight, nonsignificant increase.

Subgroups of studies

The random effects model is one method of addressing the heterogeneity of the results across studies. However, because the fixed and random effects did not yield very different results, we explored the presence of systematic variability across studies (*i.e.* differences among studies related to the study characteristics) using the fixed effects model. When the

TABLE 4. Raw data from studies

First author	Total cholesterol (mmol/L)			LDL cholesterol (mmol/L)			HDL cholesterol (mmol/L)		
	Before	Change	% change	Before	Change	% change	Before	Change	% change
Arem 90 (50)	5.34	−0.52	−10%	3.57	−0.60	−17%	1.14	0.13	11%
Arem 95 (51)	5.18	−0.41	−8%	3.50	−0.54	−15%	1.17	0	0%
Bell (52)	6.40	−0.21	−3%	NA	NA	NA	1.66	−0.26	−16%
Bogner (48)	7.17	−0.98	−14%	5.28	−0.91	−17%	1.45	−0.08	−6%
Caron (53)	5.15	0.16	3%	3.65	−0.08	−2%	1.17	0.21	18%
Cooper (12)									
T_4	6.57	−0.34	−5%	NA	NA	NA	NA	NA	NA
Placebo	6.05								
Franklyn (54)	7.41	−0.36	−5%	5.26	−0.34	6%	1.04	−0.18	−17%
Jaeschke (57)									
T_4	5.68	0.31	5%	3.64	0.18	5%	1.36	0.04	3%
Placebo	6.51			4.11			1.45		
Miura (49)	5.96	−0.13	−2%	3.76	0.16	4%	1.48	−0.08	−5%
Nilsson (55)	5.75	−0.18	−3%	NA	NA	NA	NA	NA	NA
Nyström (11)									
T_4	6.78	−0.23	3%	NA	NA	NA	NA	NA	NA
Placebo	6.67								
Paoli (58)	5.08	−0.31	−6%	3.19	−0.34	−11%	1.19	0.08	7%
Powell (56)	8.03	−0.80	−10%	4.82	−0.78	−16%	1.30	0.16	12%

NA, Data not available.

studies were divided into subgroups based on study characteristics, some of the fixed effects model heterogeneity was reduced.

Inadequately controlled hypothyroidism

Two types of mild thyroid failure patients were enrolled in the 13 studies: patients with untreated mild thyroid failure (mild patients) and patients with a history of overt hypothyroidism, but whose T_4 dose was not sufficient to normalize the serum TSH level (overt patients). Stratifying the studies according to these two types of patients created two statistically distinct groups ($P = 0.05$). The change in the serum total cholesterol concentration was much higher in the overt patient studies (−0.44 mmol/L; 95% CI, −0.18 to −0.70) than in the mild patient studies (−0.14 mmol/L, 95% CI, −0.01 to −0.28). However, the heterogeneity within the mild patient studies was of borderline significance ($P = 0.07$), suggesting that additional factors might be associated with the change in serum cholesterol concentration within this group.

Internal validity

Studies that incorporated four or more (of eight) design factors related to internal validity had a nonsignificant reduction in mean serum total cholesterol concentration (−0.04 mmol/L; 95% CI, −0.21 to 0.12), whereas the remaining studies had a larger reduction of -036 mmol/L (95% CI, −0.52 to −0.20). These two groups were significantly different ($P = 0.008$).

Other subgroups

The three randomized trials were compared with the uncontrolled studies but the two groups were not statistically different. Dividing the studies into groups according to the average age of participants, participant pretreatment TSH level, participant final TSH level, overall study score, gender representation in the study, and use of free T_4 testing for diagnosis did not divide the studies into statistically different groups.

Baseline serum total cholesterol concentration

The change in serum total cholesterol concentration and its initial level (Fig. 2) were correlated (r = 0.55). Because a change from baseline and the baseline value itself can be statistically correlated in the absence of a true association, the correlation between the sum of the pretreatment and final cholesterol levels and their difference was calculated and found to be similar (0.43) (59). Using weighted regression, the decrease in serum total cholesterol concentration was 0.04 mmol/L larger (*i.e.* −0.04 mmol/L; 95% CI, −0.08 to 0) for every 10-mg/dL increase in the baseline concentration. When controlling instead for studies that enrolled overt patients (see definition above) (50, 51) the slope increased to −0.07 mmol/L (95% CI, −0.11 to −0.02).

Combinations of groups

Dividing the sample into three mutually exclusive groups produced results similar to the regression analyses for the serum total cholesterol level, creating three statistically distinct groups: 1) studies that enrolled individuals with a history of overt hypothyroidism showed a mean serum total cholesterol reduction of −0.44 mmol/L, with a 95% CI of −0.18 to 0.70 (−17 mg/dL; 95% CI −6.9 to 27); 2) studies that did not enroll overt patients but did enroll individuals with a mean baseline serum cholesterol level more than 6.2 mmol/L (240 mg/dL) showed a mean reduction of 0.37 mmol/L, with a 95% CI of −0.15 to −0.59 (−14 mg/dL; 95% CI, −5.7 to −23); and 3) studies that did not enroll overt patients but did enroll individuals with a mean baseline serum cholesterol level 6.2 mmol/L or less (240 mg/dL) showed a mean reduction of −0.02 mmol/L, with a 95% CI of −0.18 to 0.15 (−0.7 mg/dL; 95% CI, −7.1 to 5.7).

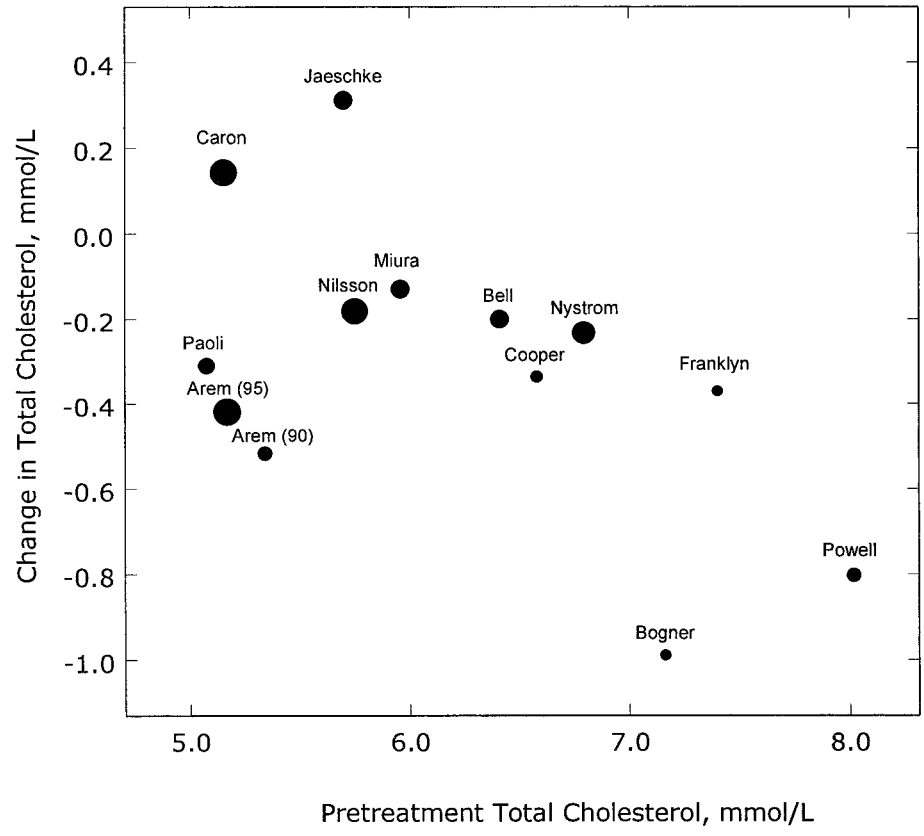

FIG. 2. Cholesterol change and pretreatment cholesterol. The relationship between the pretreatment total cholesterol level and its change for each study. Size of data point directly proportional to the reciprocal of squared SE (*i.e.* weight) of the study.

Results from excluded studies

The total cholesterol changes in the 11 excluded studies (from the 24 to which exclusion criteria were applied) ranged from −0.26 mmol/L to −2.40 mmol/L, with a median of −0.59 mmol/L (−23 mg/dL).

Comment

This critical review of the literature on the effect of T_4 in mild thyroid failure shows that 11 of 13 studies report decreases in serum total cholesterol concentration and 7 of 9 studies report decreases in serum LDL cholesterol concentration. In quantitative synthesis across these studies, the reduction in serum lipoprotein concentrations was approximately −0.20 mmol/L (−7.9 mg/dL or −5%) for total cholesterol and −0.26 mmol/L (−10 mg/dL) for LDL cholesterol. These results support the hypothesis that treating patients with mild degrees of thyroid failure will, on average, afford modest decreases in serum total and LDL cholesterol levels. Changes in serum HDL cholesterol and triglyceride levels were variable, but not statistically different from 0.

Individuals with pretreatment total cholesterol levels over 240 mg/dL seem to achieve larger reductions in the concentration of serum cholesterol, as do hypothyroid individuals taking too small a dose of T_4. This delineation is appealing because of its compatibility with current cholesterol screening guidelines that use 6.2 mmol/L as a cutoff. Furthermore, it provides an impetus to regularly monitor patients taking T_4.

These total cholesterol reductions are smaller than those suggested by another review on this topic (−0.4 mmol/L) (15). However, only eight studies (62%) are common between the analyses. Although the previous analysis has been the only review available, it does not address several important issues. Our systematic review of the treatment of mild thyroid failure and its effect on serum lipid levels incorporates additional serum lipoprotein changes, accounts for the statistical assumptions necessary for analyzing these particular studies where the necessary variances are unavailable, and, most importantly, assesses the wide differences among the various studies on this topic. This last issue is important because of the inherent difficulty in explaining the disparate results published in the literature.

Factors affecting cholesterol change

The highly variable results across studies of mild thyroid failure have sparked debate about whether serum cholesterol concentrations can be reduced with T_4 treatment. By systematically examining the characteristics among studies, it is possible to understand, and perhaps explain, much of the heterogeneity. One explanation is that there exists a relationship between the baseline concentration of serum total cholesterol and its change after the initiation of T_4 therapy, especially when the results of studies enrolling patients with suboptimally treated hypothyroidism are included in a separate stratum. This hypothesis is indirectly supported by a randomized, controlled study that enrolled hypercholesterolemic patients with normal serum TSH levels and showed

a significant total cholesterol reduction (−0.28 mmol/L) after T_4 treatment, especially for individuals with high-normal serum TSH levels (−0.74 mmol/L) (47).

Also, suboptimally treated patients with hypothyroidism may achieve larger reductions in serum total cholesterol concentrations than individuals with mild thyroid failure. This difference may be related both to differences in relative circulating concentrations of T_4 and T_3 in these thyroid states and to different rates of T_4-to-T_3 conversion in the liver and pituitary. In mild thyroid failure, thyroidal T_3 secretion is increased to compensate for falling T_4 levels. In subjects with little or no remaining thyroid gland function (*i.e.* overt hypothyroidism) this compensation mechanism is not as robust (60). Hence, the response to serum T_4 changes may be exaggerated. In addition, conversion of T_4-to-T_3 is greater in the pituitary than in the liver (61). As a result, at a given elevated TSH level, the effect of thyroid hormones in the liver, and on the LDL receptor in particular, may reflect a more severely hypothyroid state than exists in the pituitary. In combination, these lines of argument suggest that hypothyroid individuals on insufficient T_4 therapy would have a greater serum cholesterol reduction for the same T_4-induced suppression of TSH from comparably elevated TSH levels.

Limitations

Most of the studies did not include a control group. While adjustments were made for some potential confounders within these studies, the limited sample size makes simultaneous adjustment for more than two at a time problematic from a statistical viewpoint. In particular, these data cannot answer the question of whether there is an elevated level of serum TSH above which treatment is more likely to be associated with reductions in total or LDL cholesterol. Finding such thresholds requires more data than the 13 available observations. The ability to answer this kind of question is limited further because these studies describe the experiences of just 247 patients, mostly in nonrandomized designs. Larger, randomized studies would provide a firmer basis for widespread treatment recommendations and would allow for the exploration of clinically important hypotheses. Nevertheless, these studies represent the current evidence in the peer-reviewed literature on which clinicians must base their treatment decisions.

The reason for the relationship between the decrease in the serum total cholesterol level and the baseline level is uncertain. Possible explanations include statistical correlation between changes and baseline levels, regression to the mean within each study, and differences among studies in the control of other interventions (*i.e.* diet, exercise, and medications).

However, statistical correlation between changes and baseline levels has been ruled out by finding a strong correlation between change and the sum of baseline and follow-up serum cholesterol levels. Regression to the mean within studies also may not be sufficient to explain the relationship. Of the studies not enrolling previously hypothyroid patients, the only one that enrolled individuals based on a single, elevated cholesterol test (48) stands out from the rest in Fig. 2. Because regression to the mean is likely to have contributed to the large treatment effect in this particular study, that it stands out from the others suggests that any effect of regression to the mean may be small. Furthermore, three studies included control groups and would not be expected to show regression to the mean.

Other participant behavioral factors that may have caused a decline in serum lipid concentrations may have been present in some studies. Some of the studies attempted to assess diet, exercise, weight changes, and medications, but this was not universal. When the studies were stratified by the score for internal validity, the results were significantly different between the groups: the studies that attempted to control extraneous factors potentially related to cholesterol changes showed no change in total cholesterol. Studies that were less meticulous showed greater changes. Therefore, differences in the study results may be related to the degree to which each study controlled lifestyle factors (medications, diet, and exercise), incorporated randomization and control groups in the design, and treated individuals carefully with regard to dosing and length of follow-up. However, inspection of the relationship between the internal validity score and cholesterol change does not reveal a graded association, making this explanation less convincing (plot not shown).

The potential for publication bias exists. It is entirely plausible that many small studies might have never been published, which could change the results of this review. However, because the range of sample sizes is so narrow, and because most studies did not report statistically significant results, publication bias may be less likely.

Implications of treatment

The benefits of T_4 treatment have been analyzed in the context of a decision and cost-effectiveness analysis of screening for mild thyroid failure (62). In the decision model, screening was shown to be a favorable strategy because treatment yielded improvements in the symptoms associated with mild thyroid failure, prevented progression to overt hypothyroidism, and reduced serum cholesterol levels. And, although serum cholesterol reduction with T_4 was modest (4.3%) in the model, it provided an important economic benefit by decreasing the need for more expensive lipid-lowering medications. Therefore, cholesterol reduction is an important aspect of T_4 treatment, even though the benefit of reducing serum cholesterol on cardiovascular disease and mortality has not been clearly demonstrated in the population with the highest prevalence of mild thyroid failure (*i.e.* adults over age 65, especially women) (63).

One still needs to regularly monitor individuals taking T_4 to minimize the potential for iatrogenic effects (16, 64). However, a trial of Ts treatment for individuals with both elevated serum TSH and cholesterol concentrations seems to be a reasonable strategy. The potential for modest reductions in serum total and LDL cholesterol levels coupled with the potential for reducing subtle symptoms of mild thyroid failure and preventing progression to hypothyroidism provides a sound basis for considering therapy. Furthermore, careful re-titration of the T_4 dose in

patients with hypothyroidism may also have beneficial effects on serum lipids and should not be ignored.

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