Efficacy and safety of postoperative levothyroxine sodium tablets for improving serum thyroid hormone levels and tumor marker levels in patients with thyroid tumors

Dingji Hao, Linxiao Tian, Haoting He, Congru Zhu, Lili Guo, Keao Zhang, Jie Zhang

Department of Oncology, Tonglu County Hospital of Traditional Chinese Medicine, Tonglu, Zhejiang, China

Abstract

Levothyroxine tablet has been used for improving serum thyroid hormones. Despite its efficacy, there has been a persistent recurrence. We aimed to evaluate the efficacy of levothyroxine regimen (administered as sodium tablets or liquid) therapy, including the regime in combination with other thyroxine hormones, to determine its effectiveness and safety regarding thyroid tumor patient outcomes. An electronic search of the online databases (PubMed, EMBASE, and Web of Science) was performed in duplicate independently to identify any potential studies published in the English language from January 2002 to October 2022. The records were retrieved using keywords and MeSH terms. The Cochrane risk of bias tool in the Review Manager (RevMan software version 5.4.) was used to evaluate the risk of bias in the included studies. A total of 18 quality studies were reported on levothyroxine tablets. Results showed that liquid levothyroxine was more efficient than tablet levothyroxine. Further results showed that levothyroxine in combination with L-T3 or I-131 was more effective than L-T4 tablet monotherapy for improving thyroid cancer hormones. Levothyroxine tablet monotherapy is less efficient than liquid levothyroxine and/or levothyroxine combined therapy.

Key Words: levothyroxine; levothyroxine liquid; iodine (I-131); levo-thyronine (L-T4); thyroxine serum hormone; thyroid cancer.

Eur J Transl Myol 33 (3) 11582, 2023 doi: 10.4081/ejtm.2023.11582

Thyroid cancer is the most common malignant and endocrine tumor, especially around the neck regions.[1] Recently, scholars reported that over 580 000 cancer-diagnosed patients globally were thyroid cancer cases, representing about 3 percent of the overall cancer incidence rates.[2] In particular, the most common form of thyroid cancer is differentiated thyroid cancer (DTC), a category that comprises follicular thyroid carcinoma, thyroid carcinoma, and Hurthle cell carcinoma, which cumulatively causes up to 86% of thyroid cancer cases.[3] In the past few decades, DTC has exhibited an excellent prognosis accounting for between 7 and 15% of all thyroid cancer surgery.[4] However, hypothyroidism is a significant treatment conundrum in clinical outcomes as it mainly impacts the patient's physiological function. Other than unusual events of benign thyroid disease, radioiodine therapy, cancer surgery, or autoimmune thyroiditis, hypothyroidism is majorly caused by the lesions within the hypothalamic-pituitary-thyroid axis, and this leads to insufficient secretion of the crucial thyroid hormones.[5] Notwithstanding, hypothyroidism prevalence is usually determined by the serum thyroid-stimulating hormone (TSH) levels above the normal upper limits, or rather the diagnostic cut-off point (>4.0 mU/L).[5] Notably, the literature asserts that hypothyroidism is common in women and the elderly due to the inadequate action and concentration of thyroid hormones within the target tissues.[6] Initially, adjuvant radioiodine ablation, TSH suppression, and prophylactic cervical lymph node dissection were used as treatment alternatives. However, a more promising thyroid hormone replacement therapy is currently in demand as the best treatment option. The therapy has been based on a levothyroxine regimen, considered safe and effective in achieving the clinical objective of relieving DTC symptoms and normalizing the thyroid hormones to the required levels. Since TSH is asserted as the most specific and sensitive marker of thyroid tumor status in patients, the suppression of hypothyroidism symptoms is affected by levothyroxine (LT4) regimen at the serum TSH levels of 0.4 to 4.0 mU/L.[7] Although effective, the long-term supra-physiological therapy using

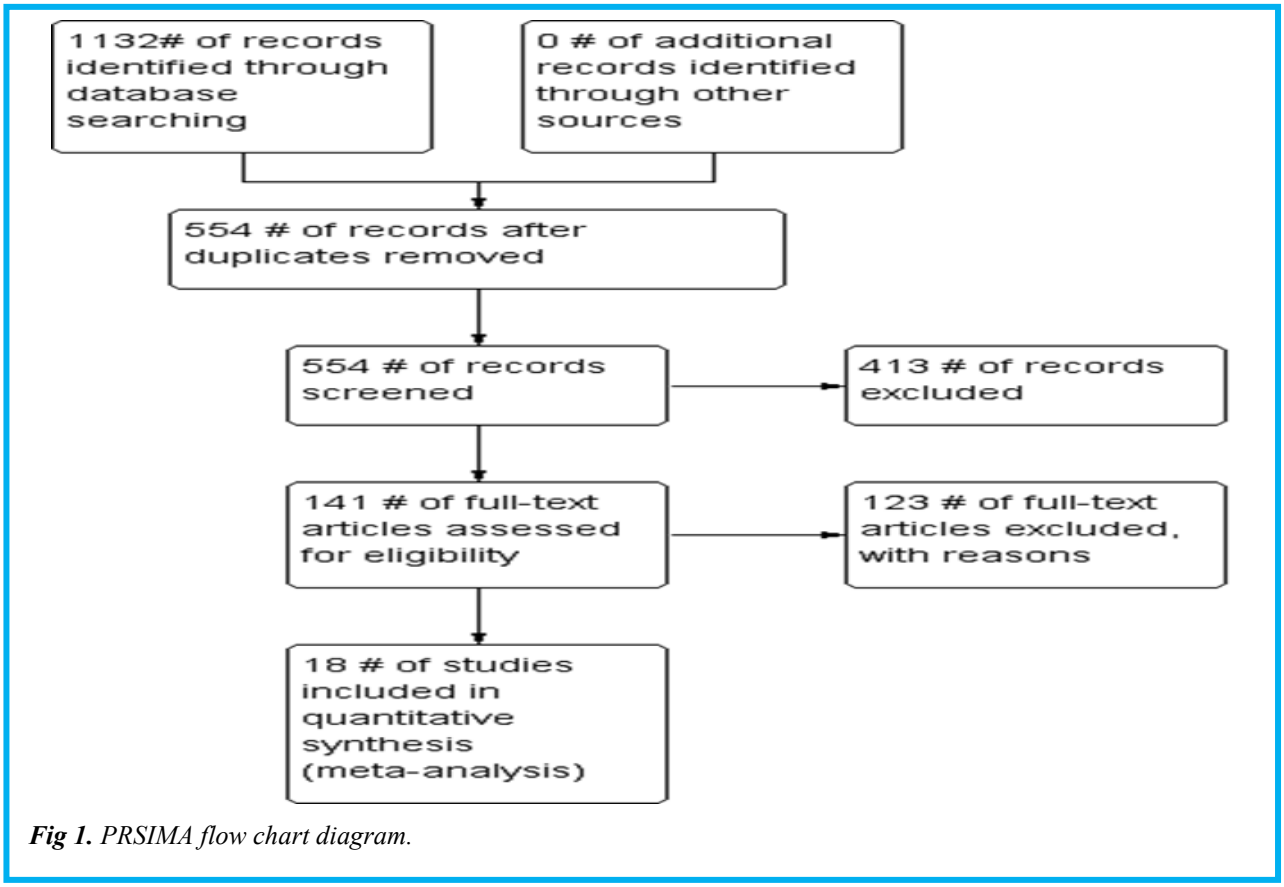

Fig 1. *PRSIMA flow chart diagram.*

levothyroxine regimes, usually as a liquid or sodium monotherapy, is currently associated with some side effects, including increased arrhythmia prevalence, reduced bone mass, and increased cardiac workload. For instance, Wiersinga et al. noted that although most patients who were on levothyroxine therapy were asymptomatic, a significant ratio (5 to 10%) exhibited residual symptoms (including troubled moods, weight gain, cognitive impairments, and fatigue, and cold intolerance) regardless of their normal thyroid test results. This brings controversies on TSH suppression therapy using levothyroxine monotherapy.[6] Additionally, the advent of the new TSH assays believed to exhibit greater sensitivity is on the debate for inclusion as a tool for evaluating TSH suppression by thyroxine hormone regimens.[8] In particular, thyroglobulin (Tg), a tissue-specific tumor marker, is poised to show a better correlation on the DTC amounts detected to inform a better treatment option. Currently, there are emerging thyroxine hormonal regimes applied for TSH suppression therapy. For instance, the routine administration of Iodine-131 (I-131) has been reported, but existing literature is yet to report its efficacy as monotherapy. [8] However, administering Iodine-131 with a follow-up of levothyroxine (L-T4), suppressive therapy is perceived to effectively improve serum TSH levels and serum thyroglobulin (Tg) levels, thus, effective DTC case management. Other regimens include a combined therapy of LT4 and liothyronine (LT3), which is argued to reduce the conversion of T4 to T3 receptors. Contrarily, other scholars assessing LT4 and LT3 combined therapy have found no significant difference with LT4 monotherapy on patient quality of life. On mood improvement, two studies have certified that combined Lt4/LT3 therapy positively improved the mood of thyroid tumor patients.[9,10] Opposition to the latter argued that the administration of LT4 monotherapy significantly reduces serum FT3 concentrations,[11] implying reduced intercellular T3 hormones in the brain and other vital organs. In this view, these scholars allude that utilizing LT3 monotherapy is likely to achieve higher intercellular T3 concentration, consequently improving the patient's quality of life.

Given the conflicting viewpoints on levothyroxine regimen towards enhancing serum TSH and Tg hormones, this systematic review and meta-analysis aimed to evaluate the efficacy of levothyroxine regimen (administered as sodium tablets or liquid) therapy, including the regime in combination with other thyroxine hormones; to determine its effectiveness and safety with regards to thyroid tumor patient outcomes.

Materials and Methods

The present systematic review and meta-analysis was done per the guidelines provided by the Cochrane Collaboration Search Strategy and Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[12]

Fig 2. *Risk of bias (Upper panel) Summary and (Lower panel) Graph.*

Eligibility criteria

Studies were included based on the following inclusion criteria:

i. Peer-reviewed articles published in English between 2002 and October 2022
ii. Prospective cohorts and randomized controlled trials
iii. Studies that compared tablet levothyroxine with liquid levothyroxine in thyroid cancer patients
iv. Studies that compared tablet levothyroxine monotherapy with combined therapy of other regiments, including iodine-13, liothyronine
v. Studies that were published in full text

Otherwise, studies were excluded if:

i. Were not published in English
ii. Were not accessible in full-text
iii. Were not RCTs and prospective cohorts
iv. Did not compare liquid vs. tablet levothyroxine or in combined therapy with other regimens

Search strategy

A manual electronic search of the online English databases (PubMed, EMBASE, and Web of Science) was performed in duplicate independently to identify any potential studies published from January 2002 to October 2022 assessing the efficacy of levothyroxine regimen administration for thyroid cancer patients. The search process entailed the use of keywords and MeSH terms that included the following; stimulating thyroid hormone (TSH), triiodothyronine (T3), free triiodothyronine (FT3), free thyroxine (FT4), levothyroxine, hypothyroidism, tablet L-thyroxine, liquid L-thyroxine, liquid L-T4, tablet levothyroxine, tablet
L-T4, thyroid cancer.

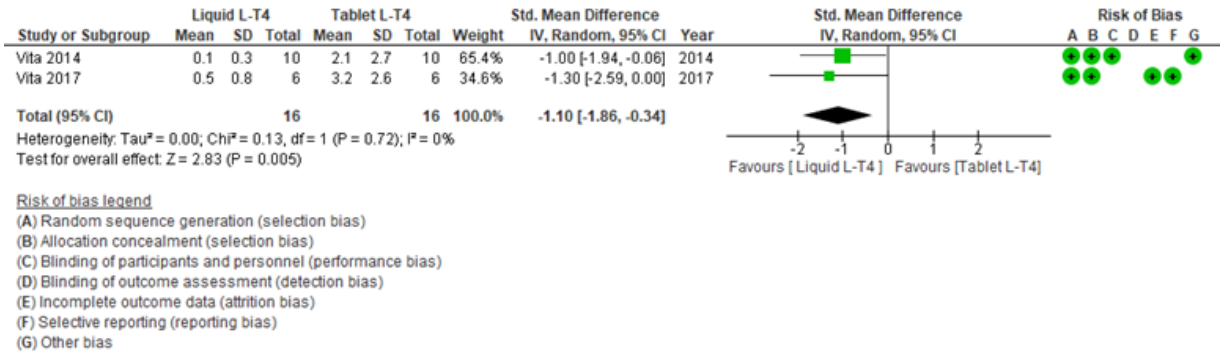

Fig 3. *Levothyroxine monotherapy or drug malabsorption: Forest plot analysis of Liquid L-T4 vs. Tablet L-T4.*

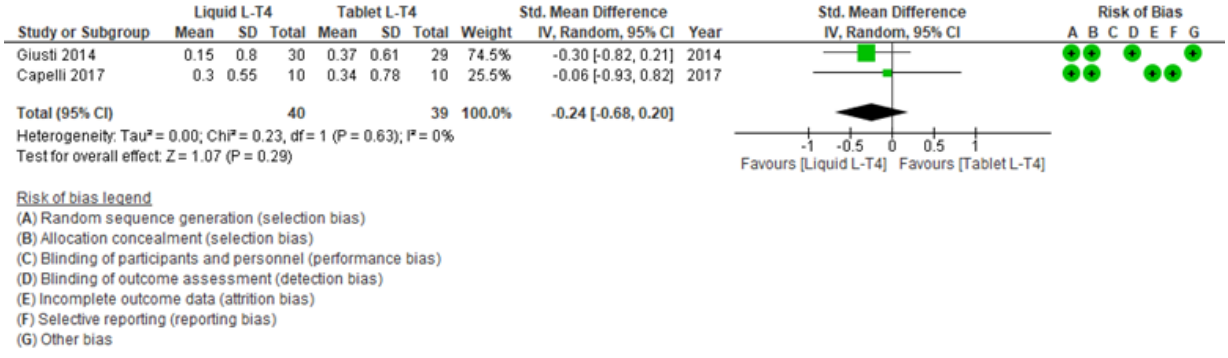

Fig 4. *Levothyroxine monotherapy for non-malabsorption: Liquid L-T4 vs. Tablet L-T4.*

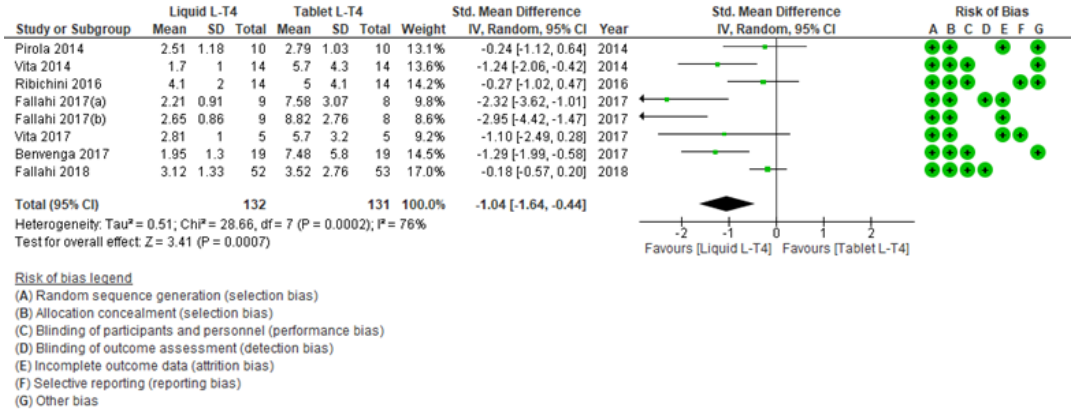

Fig 5. *TSH levels: L-T4 patients on replacement (normalization) therapy with and without drug malabsorption.*

Additionally, the reference lists of all potentially eligible studies were screened and manually retrieved for additional articles.

Study selection

All retrieved citation records were manually checked for eligibility and any record that contravened the inclusion criteria was removed. After deduplication, the reviewers independently scanned through the titles and abstracts of the articles to exclude any study that was not per the preset criteria for inclusion. It was followed by scanning and reading the full texts of the selected studies that ideally conformed to the inclusion criteria standards. Any contrary opinion regarding the inclusion or exclusion of a particular article was discussed to reach a consensus between the two reviewers. However, unresolved conflicts were addressed through a discussion with the third reviewer (G.G.T).

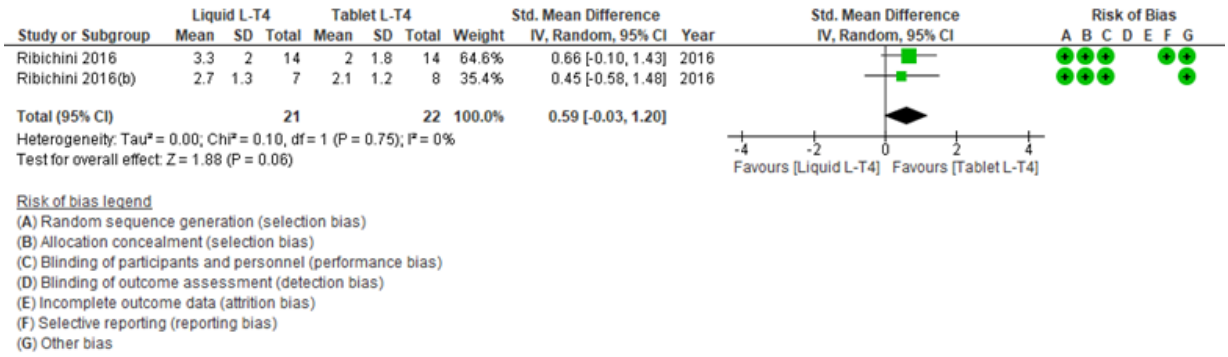

Fig 6. *TSH levels: L-T4 patients on replacement (normalization) therapy with and without drug malabsorption.*

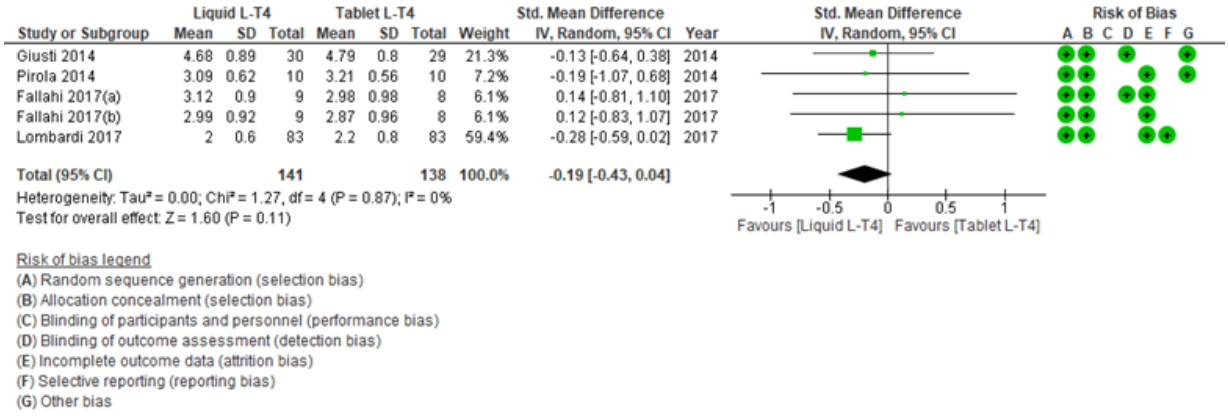

Fig 7. *Ft3 (T3) forest plot analysis.*

The data extraction process began by abstracting all relevant data on the preset datasheet. The following data were extracted from the included studies into the data sheet; first author's name, year of study publication, study design, region by country, patient demographics including age and cancer tumor type, period of study, sample size, treatment regimen, and outcome measures assessed.

Risk of bias and methodological Quality Assessment

The data quality in the included articles was analyzed using the Cochrane Risk of Bias tool through the following categories. The first was rated (good), including articles with the least bias and reported valid results with clear descriptions of participant size and populations, study settings and intervention, appropriate analytical and statistical methods, no reported study errors, and appropriate reporting of dropouts and confounding factors. The second classification was (fair); it involved studies that reported bias to a certain degree but were insufficient to invalidate the results. Also, these studies depicted suboptimal adjustments on confounder factors and may have lacked some crucial information to assess potential problems or limitations. The last category of studies (poor) data included those with significant biases that invalidated their results, i.e., studies that did not consider confounders or made appropriate adjustments. The studies might also have critical delimitations in design and analysis and missing some crucial data.

The Cochrane risk assessment tool (RevMan5.4 software) also assessed the risk of bias. The bias risk was assessed through the seven key domains: sequence generation, allocation concealment blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential sources of bias.

Statistical analyses

This study used the Cochrane Collaboration Review Manager Software (RevMan 5.4) for data and statistical analysis. The standard mean difference (SMD) was the standard measure for the overall polled effect for continuous variables when the same scale was used for the same outcome with 95% confidence intervals (CIs). The study used Cochran's Q-test with a p-value to evaluate the overall effect of the evaluated outcomes of the included articles in each meta-analysis. Besides, the I^2 statistic was used to measure heterogeneity degree, and I^2 values of 75, 50, and 25% were nominally perceived as

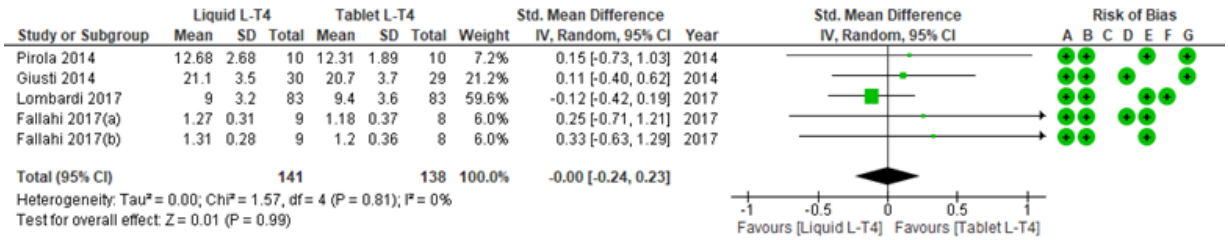

Fig 8. *Ft4 forest plot analysis outcomes.*

either high, moderate, or low heterogeneity, respectively. However, $I^2 < 50\%$ and $p > 0.1$ indicate homogeneity in the included studies.

Results

Search results

The study authors reviewed a total of 1132 articles that were retrieved from the database search. Of the total records, 578 sources were eliminated in the deduplication phase resulting in 554 records for screening. Two authors subjected the 554 records to title check and screening of the abstracts to eliminate any records contrary to the study topic. The title and abstract screening excluded 413 records; hence, only 141 sources were obtained. The final screening process involved full-text screening of all the studies to determine the suitable records for inclusion. Based on the pre-defined study eligibility criteria, 123 articles that did not meet the eligibility criteria were eliminated from the study. Finally, only 18 sources fully met the inclusion criteria and were thus considered in this study's synthesis analysis and meta-analysis. The search process results are summarized in the study PRISMA diagram (Figure 1).

Characteristics of included studies

A summary of key characteristics of the 18 included studies is presented in Supplementary Table 1. The present study borrowed extensively from all potential sources published between 2003 and 2022. Of the 18 quality studies, 12 records were comparative prospective cohort crossover studies,[13-25] while the remaining five were randomized controlled trials.[26-30] Of the included studies, eleven provided data comparisons on the effectiveness of liquid verse tablet levothyroxine, and all were based in Italy except one that was based in the United States of America.[19] The other seven studies evaluated the efficacy of levothyroxine tablets against combined therapies. Two included studies compared levothyroxine monotherapy with a combination of levothyroxine and iodine-131,[15,16] whereas five other studies evaluated levothyroxine monotherapy against LT4/LT3 combination therapy.[26-30] Of the seven studies, two were of China origin,[15,16] while the rest were from Australia,[29] Russia,[30] Brazil,[28] America,[26] and Spain.[27] Regarding patient age, most studies included adults between 18 and 78 years old, except for one study that included newborns aged between 3 to 5 days old.[14] The study included a total of 1048 participants from the studies. Most of the included studies presented a significantly smaller sample size, with the lowest being 11 and the largest 166 patients.[13]

Risk of bias assessment

All the included studies described the method of randomization and allocation concealment. Overall, the studies presented a low risk of bias in all the assessment domains. Upper and lower panels of Figure 2 present a summary of the risk of bias in all the included studies.

Levothyroxine (LT4) monotherapy: liquid L-T4 vs. tablet L-T4

TSH levels: L-T4 patients on suppressive therapy with and without drug malabsorption

The TSH levels and related outcomes on suppressive therapy patients were reported in two of the included studies. In the first study, Vita et al.[22] assessed the correct levothyroxine regimen between the liquid LT4 formulation and tablet LT4 to correct the drug intestinal malabsorption induced by proton-pump inhibitors. The results showed significantly lowered TSH levels equal to or less than the specified levels on the oral solution than the tablet LT4. Similarly, another study by Vita et al.[20] assessing the superiority of the liquid LT4 versus tablet LT4 in overcoming the co-ingestion interference induced by drug malabsorption indicated significant serum TSH reduction on the liquid LT4 suppression drugs than the tablet LT4. The results implied that liquid LT4 effectively overcame the ingestion complications from drug malabsorption. Cumulatively, for the subjects with drug malabsorption, the thyroid stimulating hormones appeared to be highly suppressed in patients receiving liquid levothyroxine than those on tablet LT4. A meta-analysis of the two studies inclusive of the 32 subjects

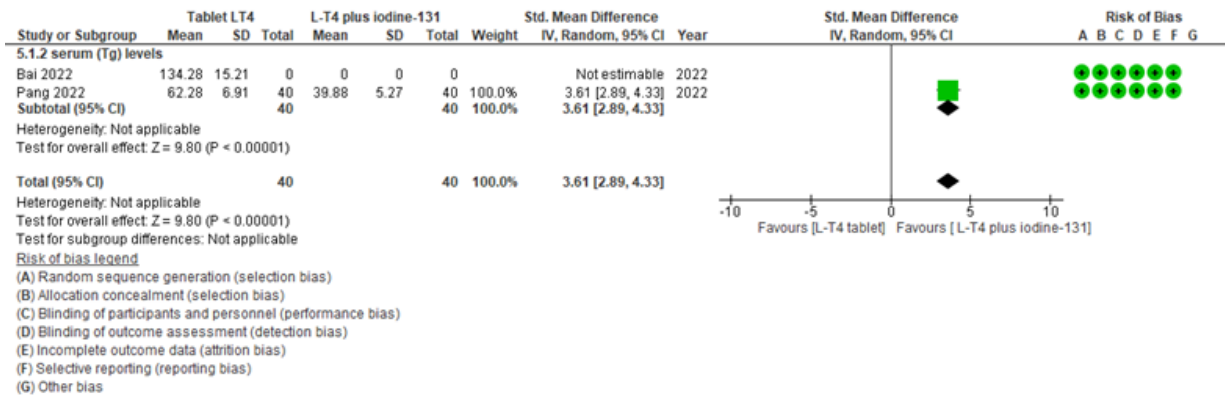

Fig 9. *Forest plot of comparison: 5 Sodium tablet LT4 vs. combined LT4 regimen, outcome: 5.1 Tablet LT4 vs. L-T4 plus iodine-131.*

showed higher suppression in the liquid than tablet regimen, expressed as standard mean difference and 95% CIs (SMD= -1.10, 95% CI= [-1.86, -0.34]; (p = 0.005). There was no heterogeneity between the included studies (Heterogeneity: Chi² = 0.13, df = 1 (p = 0.72); I² = 0%). These results are analyzed in Figure 3.

On the other hand, the TSH levels of the patients on the LT4 suppressive therapy without any drug malabsorption were also assessed. The main goal of the administration of LT4 in DTC is usually to suppress the levels of TSH. Hence, the study by Giusti et al.[23] and Cappelli et al.[13] assessed the efficacy and tolerability of the liquid LT4 formulation against the previous tablet LT4 formulation. Based on their findings, the liquid LT4 formulation resulted in a significantly higher number of thyroid cancer patients retaining required TSH levels implying that liquid LT4 did not cause variability of TSH levels. Hence, from a general point of view, patients on suppressive therapy without drug malabsorption exhibited an obvious TSH suppression with the tablet levothyroxine than those on liquid levothyroxine. In the meta-analysis of these two studies with a sample of 79 participants, the pooled results indicated a non-statistical difference between the experimental and the control group; (SMD= -0.24, 95% CI= [-0.68, 0.20], and the overall effect being 1.07 (p = 0.29). However, there was no heterogeneity between the included studies (Heterogeneity: Chi² = 0.23, df = 1 (p = 0.63); I² = 0%); (Figure 4).

TSH levels: L-T4 patients on replacement (normalization) therapy with and without drug malabsorption

Nine studies with 306 participants reported information on TSH normalization.[17, 18, 20–22, 24, 25]

In patients with drug malabsorption, the TSH was efficiently normalized in those who received liquid levothyroxine hormone compared to those who received tablet levothyroxine therapy. The pooled meta-analysis showed a statistically significant difference between the experimental group and the control group with the standard mean difference and overall effect; (SMD= -1.04 95% CI= [-1.64, -0.44]; Z = 3.41 (p = 0.0007). The included studies also reported an obvious high heterogeneity (Heterogeneity: Chi² = 28.66, df = 7 (p = 0.0002); I² = 76%) (Figure 5).

For the patients without drug malabsorption, TSH levels were remarkably improved in those who received tablet levothyroxine therapy compared to those receiving liquid levothyroxine.

The meta-analysis of the two included studies indicated no statistically significant difference between the study group and the control group (SMD= 0.59, 95% CI= [-0.03, 1.20]; with the overall effect, Z = 1.88 (p = 0.06). There was no heterogeneity among the studies (Heterogeneity: Chi² = 0.10, df = 1 (p = 0.75); I² = 0%) (Figure 6).

Ft3 (T3) and Ft4

Five included studies reported data on F-t3.[18,19,23,24] The included studies reported no significant difference in the serum Ft3 levels for the patients that received liquid levothyroxine or tablet levothyroxine.

A meta-analysis was performed using the random effect model, and the overall effect size was (SMD= -0.19, 95 % CI= [-0.43, 0.04]; (p = 0.11)). The was no heterogeneity between the sources included (Heterogeneity: Chi² = 1.27, df = 4 (p = 0.87); I² = 0%). The summarized results are shown in Figure 7.

Five more studies with a significant sample size of 279 patients provided data on serum Ft4 levels.[18,19,23,24] The pooled analysis results performed through the random effect model showed that there was no difference between the liquid thyroxine hormone and the tablet thyroxine hormone formulation (SMD = -0.00 95% CI= [-0.24, 0.23]; (p = 0.99), with no heterogeneity between the studies (Heterogeneity: Tau² = 0.00; Chi² = 1.57, df = 4 (p = 0.81); I² = 0%) (Figure 8).

Levothyroxine (LT4) tablet monotherapy versus combined regimens Sodium tablet LT4 vs. combined LT4 plus iodine-131

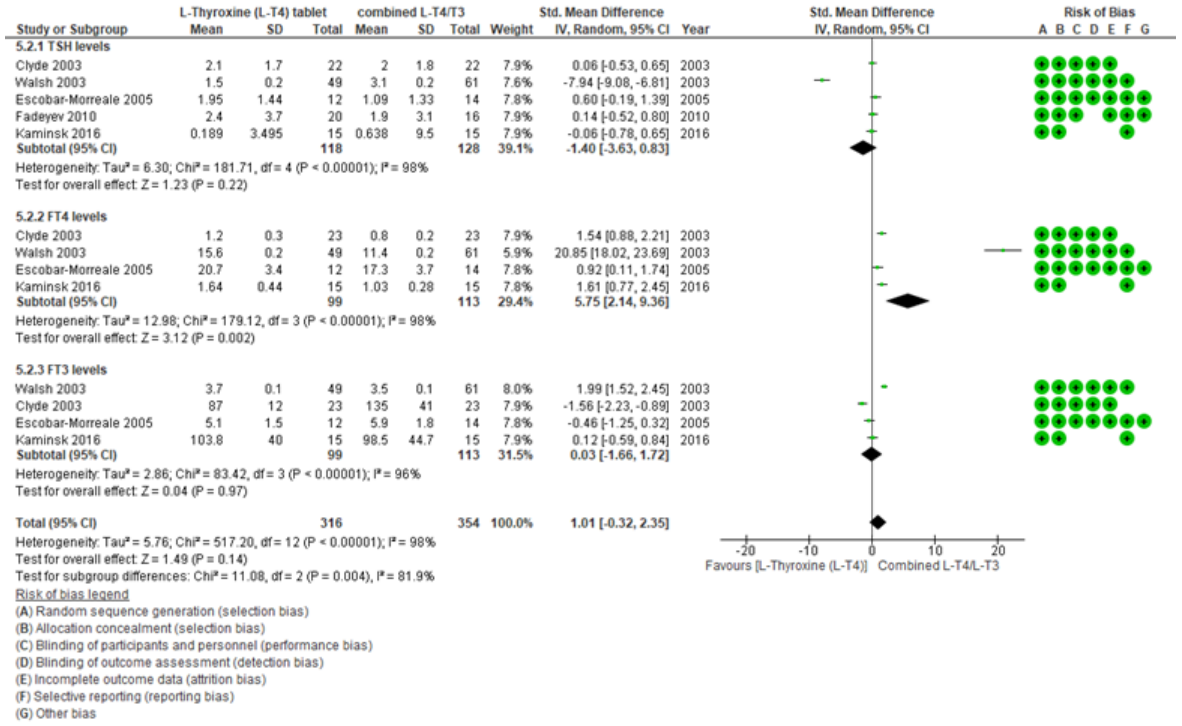

Fig 10. *Forest plot of comparison: 5 Sodium tablet LT4 vs. combined LT4 regimen, outcome: 5.2 L-Thyroxine (L-T4) vs. combined L-T4/T3.*

Regarding the clinical safety and efficacy of levothyroxine sodium tablets in improving levels, two studies investigated the effect of sodium levothyroxine tablet monotherapy compared with the levothyroxine tablet combined iodine (131).[15,16] Based on their findings, the treatment regimen of sodium levothyroxine tablets combined with iodine 131 effectively reduced the serum Tg levels implying its effectiveness over levothyroxine tablet monotherapy. Pooled-meta-analysis results showed a statistically significant difference between LT4 tablet monotherapy and the combined regimen of L-T4 and iodine-131 (SMD= 3.61, 95% CI= [2.89, 4.33], p < 0.00001) (Figure 9).

Sodium tablet LT4 vs. combined L-T4/T3.

Sodium levothyroxine tablet monotherapy was also evaluated for effectiveness compared to its combination with liothyronine for its effects on improving serum thyroid hormone levels and tumors for thyroid-tumor patients. Among the included studies, Fadeyev et al.[30] observed that there were improved profiles on serum and lipid profile levels (TSH, F4, F3) in the L-t4/T3 combined therapy compared with the L-T4 tablet monotherapy. Similar observations were made by Walsh et al.[29] who noted that a combined treatment of LT4/LT3 was effective on symptoms of hypothyroidism. On the contrary, three of the included studies evaluating the efficacy of the combined formula of LT4/LT3 demonstrated otherwise. Based on their findings, the combined therapy yielded no beneficial changes with regard to serum lipid levels in TSH or T3 levels except for free T4 levels that were lowered. With reference to the above, the pooled meta-analysis of the included studies was performed using a random effect model. The meta-analysis results showed no statistical difference in TSH between the tablet LT4 monotherapy and combined L-T4/T3 (SMD= -1.40, 95% CI= [-3.63, 0.83]; p = 0.22); but no changes or difference in FT 3 levels (SMD= 0.03, 95% CI= [-1.66, 1.72]; p = 0.97). However, for serum FT4 markers, the combined regimen was more effective in improving the serum levels than the L-T4 monotherapy (SMD = 5.75, 95% CI= [2.14, 9.36]; p = 0.002) (Figure 10 and Figure 11).

Discussion

The present systematic review and meta-analysis aimed to evaluate the safety and effectiveness of levothyroxine sodium tablets in improving TSH levels and the important markers, including Tg, fT3, and fT4, in patients with thyroid tumors. A total of 18 studies, six randomized controlled studies, and 12 prospective randomized comparative crossover design studies were included in the present meta-analysis. Levothyroxine drug therapy was evaluated on either liquid or tablet formulation for its efficacy on suppression and normalization effects on TSH and blood serum markers for thyroid cancer patients with or without drug

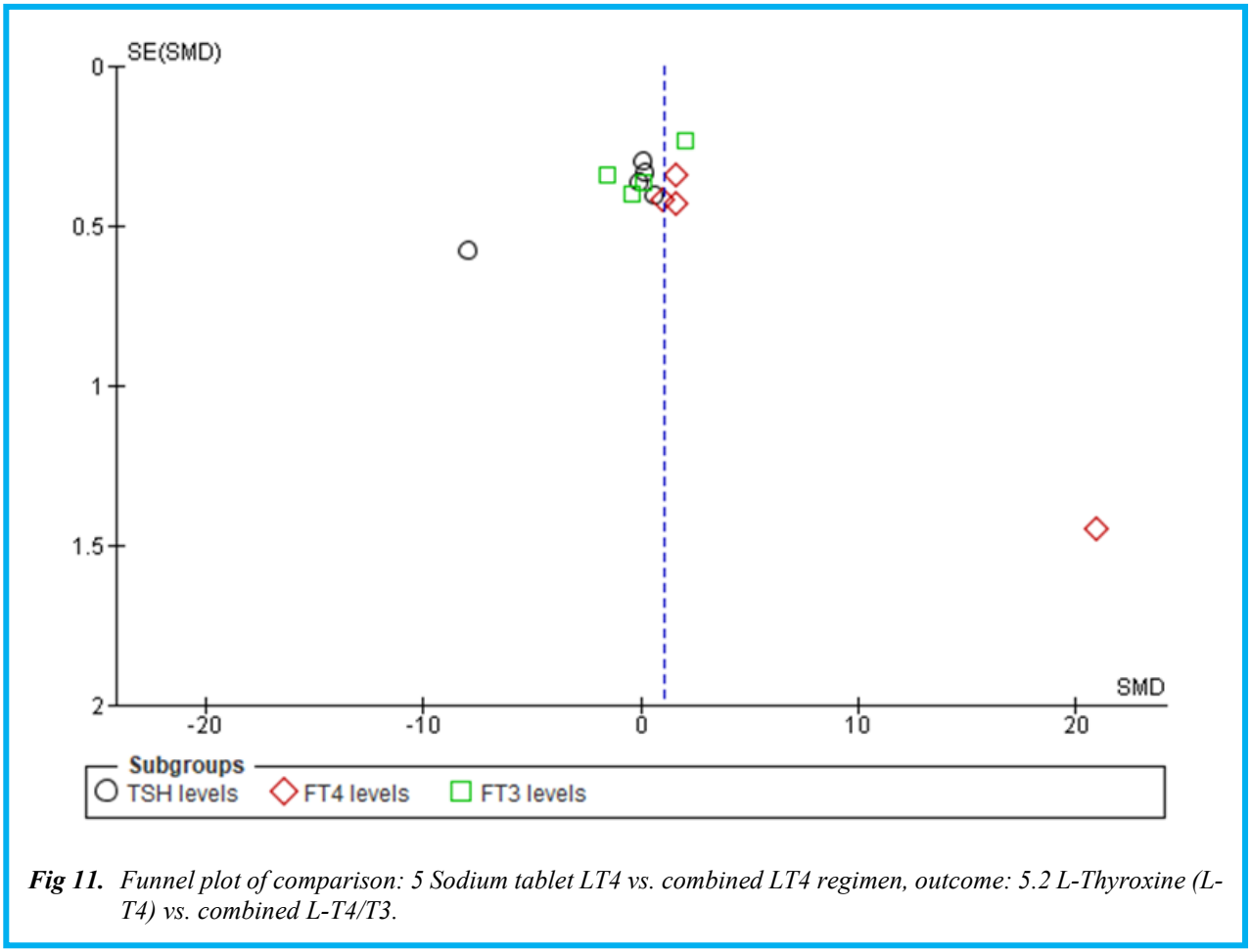

Fig 11. *Funnel plot of comparison: 5 Sodium tablet LT4 vs. combined LT4 regimen, outcome: 5.2 L-Thyroxine (L-T4) vs. combined L-T4/T3.*

abnormalities. The study also compared the potential outcomes for levothyroxine tablets with combined levothyroxine regimens of either iodine-131 for serum TSH and Tg or liothyronine for TSH, fT4, and fT3.

Thyroid cancer is among the most common endocrine tumors, accounting for more than 2 percent of all cancers.[31] About 95 percent of thyroid cancer is the follicular cell; hence, most thyroid cancer cases are DTC, followed by papillary cancer.[3,32] Differentiated thyroid cancer can trap iodine and synthesize thyroglobulin, marking the core of thyroid cancer management.[33] In addition, levothyroxine sodium (LT4) has always been used to treat thyroid cancer patients. Most patients usually attain normal blood serum levels of TSH and free T4 during treatment. Over time, the prognosis of thyroid cancer has changed well after treatment with levothyroxine tablet monotherapy; however, recurrence cases are still non-negligible. It is approximated that between 5 to 10% of patients continue to report recurring symptoms of hypothyroidism despite the fact that their serum TSH concentration is maintained in the normal required range.[33]

On the first count, the liquid levothyroxine administration was more effective than tablet levothyroxine for thyroid cancer patients on suppressive or replacement therapy with drug malabsorption. However, similar evaluation results for patients without drug malabsorption depicted non-statistically different results for liquid against tablet levothyroxine. In this accord, the study deduced that liquid levothyroxine therapy would be a more effective and safe treatment alternative for patients with drug malabsorption to improve thyroid stimulating hormones. The above study findings are supported by previous literature that identified that the liquid levothyroxine formulation attributed better therapeutic outcomes for patients subjected to concomitant multiple drug intake,[34,35] or those with *H. pylori* infection. In affirmation, proponents allude that the liquid levothyroxine pharmacokinetic properties, which do not need dissolution in the stomach at an acidic pH, unlike the tablet L-T4, is an advantage for its efficacy.[36–38] Notwithstanding, one of the included studies reinstated that the liquid levothyroxine formula was admissible even through the enteric nose tube without worrying about an empty stomach.[24] Furthermore, compared with combined therapy, the findings of the present meta-analysis demonstrated that sodium thyroxine, when combined with iodine -131was more effective in improving serum TSH and serum Tg levels than the levothyroxine therapy alone. Studies previously highlighted that iodine-131 significantly affects the treatment of thyroid cancer since it can

improve the postoperative patient prognosis and further prevent cancer metastasis and recurrence.[39,40] Moreover, since Tg produces an autoimmune antibody known as TgAb, thyroid cancer with escalating TgAb levels would attribute higher chances of recurrence; thus, the more the TgAb serum concentration, the poorer the cancer prognosis. Since TgAb is associated with Tg, Tg is thus a crucial marker of thyroid cancer secreted by malignant tumors.

Based on the findings, a significant reduction in Tg levels was achieved, depicting that levothyroxine tablets combined with iodine-131 effectively eradicated the follicular cells, thereby inhibiting stimulation of TgAb. The above is consistent with the previous findings, further associated with no adverse effects for the combined therapy.[39] The current study presents some notable limitations; hence, the interpretation of the available result and evidence should be taken care of. For instance, the study did not include large scholarly articles that compared liquid levothyroxine and tablet levothyroxine therapy and tablet levothyroxine versus combination with other hormonal drugs. Instead, this study included most studies with smaller and moderate sample sizes, which could not efficiently attribute clear representative results. Again, the included studies presented variations in their exclusion and inclusion criteria; hence, some studies' severity of thyroid cancer is inconsistent. The tools in measuring the serum TSH, fT4, and fT3 levels also varied among the included studies and could have impacted the results obtained by each study. Finally, the doses of L-T4 and LT3 also varied widely among the included studies, which might have influenced the overall results of each study. Taken together, liquid levothyroxine was more effective than tablet levothyroxine for thyroid cancer patients on suppressive or replacement therapy with drug malabsorption. However, for non-malabsorption patients, the liquid LT4 formulation resulted in a significantly higher number of thyroid cancer patients retaining required TSH levels implying that liquid LT4 did not cause variability of TSH levels. In patients with drug malabsorption, the TSH was efficiently normalized in those who received liquid levothyroxine hormone compared to those who received tablet levothyroxine therapy. Moreover, there was no significant difference in the serum Ft3 levels for the patients that received liquid levothyroxine or tablet levothyroxine. On the findings on combined therapy, sodium levothyroxine tablets combined with iodine 131 effectively reduced the serum thyroglobulin (Tg) levels, implying its effectiveness over levothyroxine tablet monotherapy. Finally, a combination of levothyroxine tablets with liothyronine showed significantly positive results on the serum and lipid profile levels (TSH, F4) compared with the L-T4 tablet monotherapy.

Hence, this study concludes that levothyroxine tablet monotherapy is less efficient than liquid levothyroxine and/or levothyroxine combined therapy. This research recommends future research using larger randomized controlled studies.

List of acronyms

RevMan - Review Manager
DTC - differentiated thyroid cancer
TSH - thyroid-stimulating hormone
LT4 - levothyroxine
Tg - thyroglobulin
I-131 - Iodine-131
LT3 - liothyronine
PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analysis
TSH - thyroid stimulating hormone
T3 - triiodothyronine
FT3 - free triiodothyronine
FT4 - free thyroxine
SMD - standard mean difference
CIs - confidence intervals

Contributions of Authors

Dingji Hao and Linxiao Tian contributed equally to this work as co-first authors. All authors read and approved the final edited typescript.

Acknowledgments

None

Funding

None

Conflict of Interest

The authors have no conflict of interest to declare.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Corresponding Author

Jie Zhang, Department of Oncology, Tonglu County Hospital of Traditional Chinese Medicine, Tonglu 311500, Zhejiang, China.
ORCID iD: *0009-0007-5943-1293*
Email : jiezhang@mailfence.com

E-mails and ORCID iD of co-authors

Dingji Hao: hdj6668882022@163.com
ORCID iD: 0009-0003-6120-6993
Linxiao Tian: tianlinxiao@163.com
ORCID iD: 0009-0007-3752-1095
Haoting He: a472905342@163.com
ORCID iD: 0009-0006-8030-0952
Congru Zhu: zcr920210@163.com
ORCID iD: 0009-0003-6883-4773
Lili Guo: 18143468892@163.com
ORCID iD: 0009-0004-4225-4989
Keao Zhang: zka88115943@163.com
ORCID iD: 0008-0005-0493-8826

References

1. Schneider DF, Chen H. New developments in the diagnosis and treatment of thyroid cancer. CA Cancer J Clin. 2013 Nov-Dec;63(6):374-94. doi: 10.3322/caac.21195. Epub 2013 Jun 24. PMID: 23797834; PMCID: PMC3800231.
2. Botta L, Gatta G, Trama A, Bernasconi A, Sharon E, Capocaccia R, Mariotto AB; RARECAREnet working group. Incidence and survival of rare cancers in the US and Europe. Cancer Med. 2020 Aug;9(15):5632-5642. doi: 10.1002/cam4.3137. Epub 2020 May 21. PMID: 32436657; PMCID: PMC7402819.
3. Haigh PI, Urbach DR. The treatment and prognosis of Hürthle cell follicular thyroid carcinoma compared with its non-Hürthle cell counterpart. Surgery. 2005 Dec;138(6):1152-7; discussion 1157-8. doi: 10.1016/j.surg.2005.08.034. PMID: 16360403.
4. Verburg FA, Mäder U, Tanase K, Thies ED, Diessl S, Buck AK, Luster M, Reiners C. Life expectancy is reduced in differentiated thyroid cancer patients ≥ 45 years old with extensive local tumor invasion, lateral lymph node, or distant metastases at diagnosis and normal in all other DTC patients. J Clin Endocrinol Metab. 2013 Jan;98(1):172-80. doi: 10.1210/jc.2012-2458. Epub 2012 Nov 12. PMID: 23150687.
5. Yoo WS, Chung HK. Subclinical Hypothyroidism: Prevalence, Health Impact, and Treatment Landscape. Endocrinol Metab (Seoul). 2021 Jun;36(3):500-513. doi: 10.3803/EnM.2021.1066. Epub 2021 Jun 18. PMID: 34139799; PMCID: PMC8258336.
6. Wiersinga WM. Adult Hypothyroidism. 2014 Mar 28. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, de Herder WW, Dhatariya K, Dungan K, Hofland J, Kalra S, Kaltsas G, Kapoor N, Koch C, Kopp P, Korbonits M, Kovacs CS, Kuohung W, Laferrère B, Levy M, McGee EA, McLachlan R, New M, Purnell J, Sahay R, Shah AS, Singer F, Sperling MA, Stratakis CA, Trence DL, Wilson DP, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000–. PMID: 25905416.7. Wilkes S, Pearce S, Ryan V, Rapley T, Ingoe L, Razvi S. Study of Optimal Replacement of Thyroxine in the ElDerly (SORTED): protocol for a mixed methods feasibility study to assess the clinical utility of lower dose thyroxine in elderly hypothyroid patients: study protocol for a randomized controlled trial. Trials. 2013 Mar 22;14:83. doi: 10.1186/1745-6215-14-83. PMID: 23522096; PMCID: PMC3617081.
8. Flux G, Leek F, Gape P, Gear J, Taprogge J. Iodine-131 and Iodine-131-Meta-iodobenzylguanidine Dosimetry in Cancer Therapy. Semin Nucl Med. 2022;52(2):167-177. doi:10.1053/j.semnuclmed.2021.11.002.
9. Lan H, Wen J, Mao Y, Huang H, Chen G, Lin W. Combined T4 + T3 therapy versus T4 monotherapy effect on psychological health in hypothyroidism: A systematic review and meta-analysis. Clin Endocrinol (Oxf). 2022 Jul;97(1):13-25. doi: 10.1111/cen.14742. Epub 2022 Apr 27. PMID: 35445422.
10. T Tariq A, Wert Y, Cheriyath P, Joshi R. Effects of Long-Term Combination LT4 and LT3 Therapy for Improving Hypothyroidism and Overall Quality of Life. South Med J. 2018 Jun;111(6):363-369. doi: 10.14423/SMJ.0000000000000823. PMID: 29863229; PMCID: PMC5965938.
11. Ito M, Takahashi S, Okazaki-Hada M, Minakata M, Kohsaka K, Nakamura T, Kasahara T, Kudo T, Nishihara E, Fukata S, Nishikawa M, Akamiuzu T, Miyauchi A. Proportion of serum thyroid hormone concentrations within the reference ranges in athyreotic patients on levothyroxine monotherapy: a retrospective study. Thyroid Res. 2022 May 10;15(1):9. doi: 10.1186/s13044-022-00127-3. PMID: 35534833; PMCID: PMC9087916.
12. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar 29;372:n71. doi: 10.1136/bmj.n71. PMID: 33782057; PMCID: PMC8005924.
13. Cappelli C, Pirola I, Gandossi E, Casella C, Lombardi D, Agosti B, Marini F, Delbarba A, Castellano M. TSH Variability of Patients Affected by Differentiated Thyroid Cancer Treated with Levothyroxine Liquid Solution or Tablet Form. Int J Endocrinol. 2017;2017:7053959. doi: 10.1155/2017/7053959. Epub 2017 May 9. PMID: 28572820; PMCID: PMC5441121.
14. Peroni E, Vigone MC, Mora S, Bassi LA, Pozzi C, Passoni A, Weber G. Congenital hypothyroidism treatment in infants: a comparative study between liquid and tablet formulations of levothyroxine. Horm Res Paediatr. 2014;81(1):50-4. doi: 10.1159/000356047. Epub 2013 Nov 12. PMID: 24247169.
15. Bai Y, Jin J, Liu Y, Zhang B, Zhang B, Li J. Effectiveness and Safety of Levothyroxine Tablets Combined with Iodine-131 in the Treatment of Thyroid Cancer. J Oncol. 2022 Jun 2;2022:3676886. doi: 10.1155/2022/3676886. PMID: 35693983; PMCID: PMC9184223.
16. Pang YL, Wang YP, Cheng K. Clinical Efficacy of Levothyroxine Sodium plus I 131 in the Treatment

of Patients with Thyroidectomy and Its Effect on the Levels of Thyroglobulin and Thyrotropin. Evid Based Complement Alternat Med. 2022 Aug 2;2022:9557061. doi: 10.1155/2022/9557061. PMID: 35958920; PMCID: PMC9363160.

17. Fallahi P, Ferrari SM, Materazzi G, Ragusa F, Ruffilli I, Patrizio A, Miccoli P, Antonelli A. Oral L-thyroxine liquid versus tablet in patients submitted to total thyroidectomy for thyroid cancer (without malabsorption): A prospective study. Laryngoscope Investig Otolaryngol. 2018 Oct 3;3(5):405-408. doi: 10.1002/lio2.186. PMID: 30410995; PMCID: PMC6209618.
18. Fallahi P, Ferrari SM, Camastra S, Politti U, Ruffilli I, Vita R, Navarra G, Benvenga S, Antonelli A. TSH Normalization in Bariatric Surgery Patients After the Switch from L-Thyroxine in Tablet to an Oral Liquid Formulation. Obes Surg. 2017 Jan;27(1):78-82. doi: 10.1007/s11695-016-2247-4. PMID: 27272506.
19. Lombardi CP, Bocale R, Barini A, Barini A, D'Amore A, Boscherini M, Bellantone R. Comparative study between the effects of replacement therapy with liquid and tablet formulations of levothyroxine on mood states, self-perceived psychological well-being and thyroid hormone profile in recently thyroidectomized patients. Endocrine. 2017 Jan;55(1):51-59. doi: 10.1007/s12020-016-1003-9. Epub 2016 Jul 7. PMID: 27388589.
20. Vita R, Di Bari F, Benvenga S. Oral liquid levothyroxine solves the problem of tablet levothyroxine malabsorption due to concomitant intake of multiple drugs. Expert Opin Drug Deliv. 2017 Apr;14(4):467-472. doi: 10.1080/17425247.2017.1290604. Epub 2017 Feb 13. PMID: 28151692.
21. Benvenga S, Di Bari F, Vita R. Undertreated hypothyroidism due to calcium or iron supplementation corrected by oral liquid levothyroxine. Endocrine. 2017 Apr;56(1):138-145. doi: 10.1007/s12020-017-1244-2. Epub 2017 Feb 3. PMID: 28155174.
22. Vita R, Saraceno G, Trimarchi F, Benvenga S. Switching levothyroxine from the tablet to the oral solution formulation corrects the impaired absorption of levothyroxine induced by proton-pump inhibitors. J Clin Endocrinol Metab. 2014 Dec;99(12):4481-6. doi: 10.1210/jc.2014-2684. PMID: 25259910.
23. Giusti M, Mortara L, Machello N, Monti E, Pera G, Marenzana M. Utility of a Liquid Formulation of Levo-thyroxine in Differentiated Thyroid Cancer Patients. Drug Res (Stuttg). 2015 Jun;65(6):332-6. doi: 10.1055/s-0034-1384535. Epub 2014 Jul 14. PMID: 25020105.
24. Pirola I, Daffini L, Gandossi E, Lombardi D, Formenti A, Castellano M, Cappelli C. Comparison between liquid and tablet levothyroxine formulations in patients treated through enteral feeding tube. J Endocrinol Invest. 2014 Jun;37(6):583-7. doi: 10.1007/s40618-014-0082-9. Epub 2014 May 1. PMID: 24789541.
25. Ribichini D, Fiorini G, Repaci A, Castelli V, Gatta L, Vaira D, Pasquali R. Tablet and oral liquid L-thyroxine formulation in the treatment of naïve hypothyroid patients with Helicobacter pylori infection. Endocrine. 2017 Sep;57(3):394-401. doi: 10.1007/s12020-016-1167-3. Epub 2016 Nov 15. PMID: 27848196.
26. Clyde PW, Harari AE, Getka EJ, Shakir KM. Combined levothyroxine plus liothyronine compared with levothyroxine alone in primary hypothyroidism: a randomized controlled trial. JAMA. 2003 Dec 10;290(22):2952-8. doi: 10.1001/jama.290.22.2952. PMID: 14665656.
27. Escobar-Morreale HF, Botella-Carretero JI, Gómez-Bueno M, Galán JM, Barrios V, Sancho J. Thyroid hormone replacement therapy in primary hypothyroidism: a randomized trial comparing L-thyroxine plus liothyronine with L-thyroxine alone. Ann Intern Med. 2005 Mar 15;142(6):412-24. doi: 10.7326/0003-4819-142-6-200503150-00007. PMID: 15767619.
28. Kaminski J, Miasaki FY, Paz-Filho G, Graf H, Carvalho GA. Treatment of hypothyroidism with levothyroxine plus liothyronine: a randomized, double-blind, crossover study. Arch Endocrinol Metab. 2016 Nov-Dec;60(6):562-572. doi: 10.1590/2359-3997000000192. Epub 2016 Aug 25. PMID: 27982198.
29. Walsh JP, Shiels L, Lim EM, Bhagat CI, Ward LC, Stuckey BG, Dhaliwal SS, Chew GT, Bhagat MC, Cussons AJ. Combined thyroxine/liothyronine treatment does not improve well-being, quality of life, or cognitive function compared to thyroxine alone: a randomized controlled trial in patients with primary hypothyroidism. J Clin Endocrinol Metab. 2003 Oct;88(10):4543-50. doi: 10.1210/jc.2003-030249. PMID: 14557419.
30. Fadeyev VV, Morgunova TB, Melnichenko GA, Dedov II. Combined therapy with L-thyroxine and L-triiodothyronine compared to L-thyroxine alone in the treatment of primary hypothyroidism. Hormones (Athens). 2010 Jul-Sep;9(3):245-52. doi: 10.14310/horm.2002.1274. PMID: 20688622.
31. Bikas A, Burman KD. Epidemiology of Thyroid Cancer. In: Markus Luster, Leonidas H. Duntas, Leonard Wartofsky (Eds.), The Thyroid and Its Diseases, 541-547 - January 2019. doi: 10.1007/978-3-319-72102-6_35
32. Lundgren CI, Hall P, Dickman PW, Zedenius J. Clinically significant prognostic factors for differentiated thyroid carcinoma: a population-based, nested case-control study. Cancer. 2006 Feb

1;106(3):524-31. doi: 10.1002/cncr.21653. PMID: 16369995.
33. Jonklaas J, Bianco AC, Cappola AR, Celi FS, Fliers E, Heuer H, McAninch EA, Moeller LC, Nygaard B, Sawka AM, Watt T, Dayan CM. Evidence-Based Use of Levothyroxine/Liothyronine Combinations in Treating Hypothyroidism: A Consensus Document. Eur Thyroid J. 2021 Mar;10(1):10-38. doi: 10.1159/000512970. Epub 2021 Feb 16. PMID: 33777817; PMCID: PMC7983670.
34. Kwiatek MA, Roman S, Fareeduddin A, Pandolfino JE, Kahrilas PJ. An alginate-antacid formulation (Gaviscon Double Action Liquid) can eliminate or displace the postprandial 'acid pocket' in symptomatic GERD patients. Aliment Pharmacol Ther. 2011 Jul;34(1):59-66. doi: 10.1111/j.1365-2036.2011.04678.x. Epub 2011 May 3. PMID: 21535446; PMCID: PMC3612878.
35. Virili C, Brusca N, Capriello S, Centanni M. Levothyroxine Therapy in Gastric Malabsorptive Disorders. Front Endocrinol (Lausanne). 2021 Jan 28;11:621616. doi: 10.3389/fendo.2020.621616. PMID: 33584549; PMCID: PMC7876372.
36. Nagy EV, Perros P, Papini E, Katko M, Hegedüs L. New Formulations of Levothyroxine in the Treatment of Hypothyroidism: Trick or Treat? Thyroid. 2021 Feb;31(2):193-201. doi: 10.1089/thy.2020.0515. Epub 2020 Nov 2. PMID: 33003978.
37. Trimboli P, Mouly S. Pharmacokinetics and Clinical Implications of Two Non-Tablet Oral Formulations of L-Thyroxine in Patients with Hypothyroidism. J Clin Med. 2022 Jun 16;11(12):3479. doi: 10.3390/jcm11123479. PMID: 35743549; PMCID: PMC9224574.
38. Morelli S, Reboldi G, Moretti S, Menicali E, Avenia N, Puxeddu E. Timing of breakfast does not influence therapeutic efficacy of liquid levothyroxine formulation. Endocrine. 2016 Jun;52(3):571-8. doi: 10.1007/s12020-015-0788-2. Epub 2015 Nov 4. PMID: 26537478.
39. Morelli S, Reboldi G, Moretti S, Menicali E, Avenia N, Puxeddu E. Timing of breakfast does not influence therapeutic efficacy of liquid levothyroxine formulation. Endocrine. 2016 Jun;52(3):571-8. doi: 10.1007/s12020-015-0788-2. Epub 2015 Nov 4. PMID: 26537478.
40. Fard-Esfahani A, Emami-Ardekani A, Fallahi B, Fard-Esfahani P, Beiki D, Hassanzadeh-Rad A, Eftekhari M. Adverse effects of radioactive iodine-131 treatment for differentiated thyroid carcinoma. Nucl Med Commun. 2014 Aug;35(8):808-17. doi: 10.1097/MNM.0000000000000132. PMID: 24751702.

Disclaimer

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article or claim that may be made by its manufacturer is not guaranteed or endorsed by the publisher.

Submission: July 11, 2023
Revision received: July 15, 2023
Accepted for publication: July 15, 2023

Supplemental Table 1. Summary of Included Studies.

Authors (year)	Setting & Country	Targeted study population	Treatment groups & regimen	Sample size (n); (T/C)	Outcomes assessed
Ribichini et al., 2016	Hospital outpatient unit, Italy	naïve hypothyroid patients	Liquid L-T4 Vs. Tablet L-T4	47 (28/15)	Serum TSH levels
Vita et al., 2017	Italy	Patients on L-T4 replacement or suppressive therapy	Liquid L-T4 Vs. Tablet L-T4	11	Serum TSH Thyroid stimulating hormone
Vita et al., 2014	Italy	patients on L-T4 replacement or suppressive therapy	Liquid L-T4 Vs. Tablet L-T4	24	serum TSH
Pirola et al.2014	Italy	Patients with total thyroidectomy (laryngeal cancer)	Liquid L-T4 (Group T)vs. tablet L-T4 (Group L)	20 (10/10)	TSH, fT4 and fT3
Giusti et al. 2014	Italy	patients with differentiated thyroid cancer (after surgery)	Liquid L-T4 Vs. Tablet L-T4	59	thyroid stimulating hormone (TSH) levels
Fallahi et al. 2017	Italy	hypothyroid patients	Liquid L-T4 Vs. Tablet L-T4	17	TSH, free T3 (FT3), free T4 (FT4)
Benvenga	Italy	Hypothyroid patients	Liquid L-T4	19	TSH

et al., 2017			Vs. Tablet L-T4		
Lombardi et al.,2017	Endocrine Surgery Unit, United States	thyroidectomized patients	Liquid L-T4 Vs. Tablet L-T4	166 (83/83)	TSH, free T3 (FT3), free T4 (FT4)
Capelli et al. 2017	Italy	patients with differentiated thyroid cancer (after surgery)	Liquid L-T4 Vs. Tablet L-T4	102 (51/51)	TSH
Peroni et al., 2014	Italy	Patients with congenital hypothyroidism (CH)	Liquid L-T4 Vs. Tablet L-T4	78 (36/36)	Thyroid-stimulating hormone (TSH) and free thyroxine (fT4) , Developmental quotient (DQ)
Fallahi et al., 2018	Italy	patients without malabsorption after thyroidectomy	Liquid L-T4 Vs. Tablet L-T4	105 (52/53)	TSH FT4 and FT3 levels
Pang et al., 2022	China	DTC patients who required thyroidectomy after surgery	levothyroxine sodium tablets vs. levothyroxine sodium treatment plus I 131	80 (40/40)	Serum Tg and (TSH) levels.
Bai et al., 2022	China	thyroid cancer patients receiving radical thyroidectomy	levothyroxine tablets vs levothyroxine tablets combined	70 (35/35)	serum (Tg) and (TgAb) levels