Efficacy and Safety of Once Weekly Thyroxine as Compared to Daily Thyroxine in Managing Primary Hypothyroidism: A Systematic Review and Meta-Analysis

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Abstract

Aims: No meta-analysis is available which has holistically analyzed efficacy and safety of once weekly thyroxine (OWT) vs. standard daily therapy (SDT) with regards to managing primary hypothyroidism. We undertook this meta-analysis to address this knowledge gap.

Methods: Electronic databases were searched for clinical trials involving hypothyroid patients receiving OWT in intervention arm, and SDT in control arm. Primary outcome was to evaluate changes in serum thyroid stimulating hormone. Secondary outcomes were to evaluate alterations in total tetra-iodothyronine (TT4), total tri-iodothyronine (TT3), free T4 (FT4), free T3 (FT3), heart rate (HR), cardiac function, symptomatology, and adverse events.

Results: From initially screened 159 studies, data from four trials involving 294 patients were analyzed. Patients of OWT had significantly higher thyroid stimulating hormone (TSH) [mean difference (MD) +1.85 mU/L (95% confidence interval, CI: 0.95–2.75); P < 0.01; I² = 63%], comparable TT4 [MD -0.87 mcg/dl (95% CI: -2.98–1.24); P = 0.42; I² = 65%], and significantly lower TT3 [MD -15.7 ng/dl (95% CI: -29.9–1.51); P = 0.03; I² = 90%], following 6-weeks therapy. TT4 [MD 3.05 mcg/dl (95% CI: 1.44–4.66); P < 0.01, and FT4 [MD 0.56 ng/dl (95% CI: 0.04–1.08); P = 0.03; I² = 66%] were significantly higher 2 h after thyroxine intake, in people on OWT as compared to SDT. TT4 levels were significantly higher 4 h after thyroxine intake in OWT as compared to SDT [MD 0.70 ng/dl (95% CI: 0.52–0.88); P < 0.01]. Following 4–8 h of intake of thyroxine, isovolumetric contraction time [MD 3.62 ms (95% CI: 1.93–5.31); P < 0.01; I² = 0%] and aortic ejection time/pre-ejection period ratio [MD 0.01 (95% CI: 0.00–0.02); P = 0.02; I² = 0%] were significantly higher in people on OWT as compared to SDT.

Conclusion: OWT is associated with less efficient control of hypothyroidism at 6 weeks and may be associated with supraphysiologic elevation of thyroid hormone levels along with transient echocardiographic changes in some patients following 2-4 h of thyroxine intake.

Keywords: Daily thyroxine, hypothyroidism, weekly thyroxine

INTRODUCTION

The most common cause of poor control of hypothyroidism is noncompliance to daily thyroxine therapy.[1] For best results, patients are advised to take thyroxine daily empty stomach, with at least 1 h gap between any food intake and thyroxine ingestion for optimal absorption, which many patients find difficult to follow over prolonged periods of time.[1,2] The need to keep thyroxine intake away from other medications, which the patient might be taking, further complicates the matter.[2] Commonly used medicines which impair thyroxine absorption from the gastrointestinal tract include antacids, calcium, and iron supplements.[2] Poor understanding of such issues often leads to over replacement of thyroxine by the treating doctor, resulting in fluctuations of TSH from low to normal to even high levels (brittle hypothyroidism).[3] Few studies have
suggested that once weekly directly observed thyroxine therapy to improve compliance, translates into a better and more smooth control of hypothyroidism in patients having poorly compliant brittle hypothyroidism.\(^4,^5\) The American Thyroid Association has recommended once weekly thyroxine (OWT) therapy for the elderly population and for patients who are dependent on caregivers for their medication intake.\(^6\) There have been several small trials evaluating the role of OWT in managing hypothyroidism.\(^4,^5\) Concerns have been raised that OWT may lead to higher supraphysiologic levels of thyroxine in the initial few days after intake of a large dose of OWT, which may have an adverse impact on cardiovascular function. Also, it is feared that by the 6th day of thyroxine intake, the efficacy of OWT may wear off leading to reappearance of symptoms of hypothyroidism and fluctuations in TSH levels. However, till date, no meta-analysis is available evaluating the efficacy and safety of OWT in managing hypothyroidism. Hence, the aim of this meta-analysis was to evaluate the efficacy and safety of OWT in managing primary hypothyroidism.

**Methods**

The meta-analysis was carried out according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions.\(^6\) The predefined protocol has been registered in PROSPERO having Registration number of CRD42020190008. All randomized and non-randomized controlled trials (RCTs) published till March 2020 were considered for this meta-analysis. This meta-analysis has been reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses, the filled checklist of which can be found at the end of the manuscript.\(^7\) Since ethical approval already exists for the individual studies included in the meta-analysis, no separate approval was required for this study.

The PICOS criteria was used to screen and select the studies for this meta-analysis with patients (P) being people living with primary hypothyroidism; intervention (I) being use of OWT for managing hypothyroidism; control (C) being patients on standard daily thyroxine (SDT) for managing hypothyroidism; outcomes (O); and study design (S) being evaluated were impact on serum TSH, total tetra-iodothyronine (TT4) levels, total tri-iodothyronine (TT3) levels, HR, cardiac function, and thyroid symptomatology. Only patients with primary hypothyroidism were considered for this meta-analysis. Only those studies were included in this meta-analysis which had at least two treatment arms/groups, with one of the groups having patients with primary hypothyroidism receiving OWT therapy and the other arm/group receiving SDT therapy. This meta-analysis intended to evaluate the efficacy and safety of OWT in managing primary hypothyroidism.

The primary outcome was to evaluate the changes in serum TSH. The secondary outcomes of this study were to evaluate the alterations in TT4, TT3, free T4, free T3, HR, cardiac function (assessed by echocardiography), thyroid symptomatology, discontinuation of medication due to adverse events, and any other adverse events as described by authors.

**Search method for identification of studies**

The electronic databases of Medline (Via PubMed), Embase (via Ovid SP), Cochrane central register of controlled trials (CENTRAL) (for trials only), ctri.nic.in, clinicaltrials.gov, global health, and Google scholar were searched in detail using a Boolean search strategy: ((weekly thyroxine) OR (OWT*) OR (intermittent thyroxine*)) AND ((hypothyroidism) OR (primary hypothyroidism)) [Figure 1].

**Data extraction and study selection**

Data extraction was carried out independently by two authors using standard data extraction forms. In cases where more than one publication of a single study group were found, results were grouped together and relevant data from each report were used in the analyses. Data on the primary and secondary outcomes as stated above were extracted. Patient characteristics (including demographic information and comorbidities) from the different studies included and excluded from the analysis were noted in a tabular form [Tables 1 and 2]. All disagreements were resolved by the fifth and sixth authors.

**Assessment of risk of bias in included studies**

Three authors independently assessed the risk of bias using the risk of bias assessment tool in Review Manager (Revman) Version 5.3 (The Cochrane Collaboration, Oxford, UK 2014) software. The following points were taken into consideration namely, was there adequate sequence generation (selection bias), whether the allocation was adequately concealed (selection bias), or whether the knowledge of the allocated...
### Table 1: Baseline characteristics of included studies

| Author, year (ref) | Jayakumari et al., 2019[8] | Rajput et al., 2017[9] | Bornschein et al., 2012[4] | Grebe et al., 1997[5] |
|--------------------|---------------------------|------------------------|----------------------------|-----------------------|
| Study design       | Open-label prospective controlled study | Randomized crossover study | Randomized crossover study | Randomized crossover study |
| Site               | Thiruvananthapuram, India | Rohtak, India           | Curitiba, Brazil            | Wellington, New Zealand |
| Participants       | Patients taking levothyroxine >5 mcg/kg/d with or without normalization of TSH (considered “thyroxine-resistant hypothyroidism” in this study) | Hypothyroid patients, biochemically euthyroid on stable doses of LT4 for at least 3 months | Hypothyroid patients, biochemically euthyroid on stable doses of LT4 for at least 3 months | Hypothyroid patients, on stable doses of LT4 for at least 3 months |
| Duration           | 12-week intervention and 12 weeks follow up | 6-weeks initially and 6 weeks after crossover | 6-weeks initially and 6 weeks after crossover | 6-weeks initially and 6 weeks after crossover |
| Intervention (OWT) | 1.7 mcg/kg/d of thyroxine needed for 7 days and rounded off to closest 50 mcg | Seven times the previous daily dose | Seven times the previous daily dose | Seven times the previous daily dose |
| Control (SDT)      | Continue previous LT4 dose or a smaller dose (not less than 1.7 mcg/kg/d) | Continue previous LT4 dose | Continue previous LT4 dose | Continue previous LT4 dose |
| N (OWT/SDT)        | 52 (34/18)                  | 100 (50/50)             | 14 (6/8)                   | 12 (5/7)               |
| Outcomes measured  | TSH, T4, T3, fT3, fT4       | TSH, T4, T3, QoL, HSS   | TSH, fT4, TT3, Systolic function by 2D-echo*, HSS | TSH, fT4, fT3, rT3, TBG, thyroid symptoms, lipids, ALT, AST, GGT, ALP, Osteocalcin, Systolic time interval by 2D-echo 50.8±14.5 |
| Age (years)        | 33.2±9.3                    | 35.4±8.4                | 42.5±7.48                  | (NA group-wise)        |
| Weight (kg)        | 35.6±12.7                   | 36.1±10.7               | 41.2±8.41                  | NA                    |
| BMI (kg/m2)        | 61.95±16.2                  | 64.5±9.0                | NA                         | NA                    |
| Pulse Rate, beats/min | 25.03±5.4              | 26.1±3.0                | NA                         | NA                    |
| Duration of hypothyroidism (yrs) | 11.2±8.0                 | 11.1±7.2                | NA                         | NA                    |
| TSH (mIU/L)        | 31.3 (17.5 – 53.2)          | 2.6±1.4                 | 2.3±1.37                   | NA                    |
| TT4 (mcg/dl)       | 36.5 (23.8 – 53.3)          | 2.5±1.4                 | 2.39±1.19                  | NA                    |
| OWT:               | 7.5±2.9                     | 9.3±1.2                 | 9.6±1.5                    | NA                    |
| SDT:               | 8.8±7.43                    | 8.9±7.43                | 1.6±0.35                   | (NA group-wise)       |
| fT4 (ng/dl)        | NA                          | NA                      | 1.13±0.15                  | NA                    |
| Dose of LT4 given (mcg/kg/day) | 1.8±0.7                  | NA                      | 1.12±0.17                  | NA                    |
| OWT:               | 2.31±0.03                   | NA                      | 1.22±0.08                  | (NA group-wise)       |
| SDT:               | NA                          | NA                      | 1.11±0.14                  | NA                    |

HSS: Hyperthyroid symptom score. *Systolic function was analyzed by: pre-ejection period (PEP), aortic ejection time (ET), isovolumetric contraction time (ICT), and heart rate (HR)
interventions was adequately prevented during the study or not. Participants and personnel (performance bias) blinding was specifically looked for and so was the blinding of the outcome assessors (detection bias). We looked for whether the incomplete outcome data issue was adequately addressed or not (attrition bias). Are reports of the study free of suggestion of selective outcome reporting (reporting bias), was also evaluated. Lastly, we also looked for whether the study was apparently free of other problems that could put it at a risk of bias. Any disagreements were resolved by the fourth author.

Quality assessment of the included studies was also conducted using the Jadad scale. The Jadad scale consists of three domains: randomization (0–2 points), blinding (0–2 points), and an account of all patients (0–1 point). We classified the quality of RCTs as good (4–5 points), fair (3 points), or poor (0–2 points).

**Measures of treatment effect**

For continuous variables, the outcomes were expressed as mean differences (MDs) with 95% CI. Conventional units were used for analysis, and all studies reporting results in SI units were converted to conventional units for analysis. For dichotomous outcomes (treatment success/restoration of euthyroidism) results were expressed as risk ratios (RR) with 95% CI. For adverse events, results were expressed as posttreatment absolute risk differences. RevMan 5.3 was used for comparing MD of the different primary and secondary outcomes between the OWT and SDT groups of the included studies.

**Assessment of heterogeneity**

Heterogeneity was initially assessed by studying the forest plot generated for the primary and secondary outcomes of this study. Subsequently heterogeneity was analyzed using a Chi² test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the $I^2$ test. The interpretation of $I^2$ values is as follows: 0–40%: might not be important; 40–60%: may represent moderate heterogeneity; 60–90%: may represent substantial heterogeneity; 90–100%: considerable heterogeneity. The importance of the observed value of $I^2$ depends on the magnitude and direction of treatment effects and the strength of the evidence for heterogeneity (e.g. $P$ value from the Chi² test, or a confidence interval for $I^2$).

**Grading of the results**

An overall grading of the evidence related to each of the primary and secondary outcomes of the meta-analysis was done using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach. The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of
bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates, and risk of publication bias.[15] The GRADEpro Guideline Development Tool (GDT) software (McMaster University and Evidence Prime Inc, 2015) was used to create the Summary of Findings (SoF) table in this meta-analysis [Table 3]. Publication bias was assessed by plotting the Funnel Plot, which specifically targets small study bias, in which small studies tend to show larger estimates of effects and greater variability than larger studies.[16] Presence of one or more of the smaller studies outside the inverted funnel plot was taken as evidence of presence of significant publication bias.[16]

Data synthesis
Data were pooled as random effect model for the analysis of primary and secondary outcomes. The outcomes were expressed as 95% CI. Forrest plots were plotted with left side of the graph favouring OWT and right side of the graph favoring control (SDT) using RevMan 5.3 software. P < 0.05 was considered statistically significant.

Results
A total of 159 articles were found in the initial search [Figure 1]. Following screening of the titles, abstracts, followed by full-texts, the search was reduced down to nine studies which were evaluated for inclusion in this meta-analysis. Three RCTs (Bornschein et al,[5] Grebe et al,[5] Rajput et al[9]), and one non RCT Jayakumari et al,[9] which fulfilled all criteria were analyzed in this meta-analysis. Two studies were excluded as they did not have a valid control group (Walker et al,[13] and Wasoori et al[11]). Two studies were excluded as they evaluated alternate day levothyroxine therapy instead of OWT (Dayal et al,[12] and Jhavar et al[10]). One study was excluded as it evaluated twice weekly therapy instead of OWT (Taylor et al,[14]). The details of all the studies included and excluded in this meta-analysis have been elaborated in Tables 1 and 2 respectively.

Risk of bias in the included studies
The summaries of risk of bias of the four studies included in the meta-analysis have been elaborated in Figure 2a, 2b and Supplementary Table 1. Random sequence generation and performance bias were judged to be at low risk of bias in three out of four studies (75%). Allocation concealment (selection bias) was at low risk in one out of four studies (25%). Blinding of outcome assessment (detection bias) was low risk in two out of four studies (50%). Source of funding, especially pharmaceutical, authors from the pharmaceutical organizations and conflict of interests were looked into the “other bias” section. All the four studies had low attrition bias, reporting bias and other biases. Among the 4 studies evaluated in this meta-analysis, one was of good quality, and 3 were of poor quality as evaluated by the Jadad scale [Supplementary Table 2].

Table 3: Summary of findings

| Outcomes                              | Anticipated absolute effects (95% CI) | No of participants (studies) | Certainty of the evidence (GRADE) |
|---------------------------------------|--------------------------------------|-----------------------------|----------------------------------|
| TSH (thyroid stimulating hormone) (6 weeks) | ?                                    | 294 (4 RCTs)                  | ⬠⬠⬠⬠ HIGH                      |
| Total T4 (6 weeks)                    | MD 1.85 mU/L higher (0.95 higher to 2.75 higher) | 242 (2 RCTs)                  | ⬠⬠⬠ MODERATE               |
| Total T3 (6 weeks)                    | MD 0.87 mcg/dl lower (2.98 lower to 1.24 higher) | 218 (2 RCTs)                  | ⬠⬠⬠ MODERATE               |
| Total T4 (2 h)                        | MD 15.7 ng/dl lower (29.9 lower to 1.51 lower) | 52 (1 RCT)                   | ⬠⬠⬠ MODERATE               |
| Total T3 (2 h)                        | MD 3.05 mcg/dl higher (1.44 higher to 4.66 higher) | 80 (2 RCTs)                   | ⬠⬠⬠ MODERATE               |
| Total T4 (2 h)                        | MD 3.79 ng/dl higher (4.53 higher to 12.11 higher) | 52 (2 RCTs)                   | ⬠⬠⬠ MODERATE               |
| Free T4 (4 h)                         | MD 0.7 ng/dl higher (0.52 higher to 0.88 higher) | 52 (2 RCTs)                   | ⬠⬠⬠ MODERATE               |
| Aortic Ejection Time (4-8 h)          | MD 6.41 ms lower (13.8 lower to 0.99 higher) | 52 (2 RCTs)                   | ⬠⬠⬠ MODERATE               |
| Isovolumetric Contraction Time (4-8 h) | MD 3.62 ms higher (1.93 higher to 5.31 higher) | 52 (2 RCTs)                   | ⬠⬠⬠ MODERATE               |
| AET/PEP (4-8 h)                       | MD 0.01 higher (0 to 0.02 higher) | 52 (2 RCTs)                   | ⬠⬠⬠ MODERATE               |

Funnel plot is suggestive of presence of most of the studies outside the plot, hence it is likely that significant publication bias is present

TSH: Thyroid stimulating hormone; RCT: Randomized controlled trial
Effect of once weekly thyroxine on primary outcomes

**Thyroid stimulating hormone**

Four studies with 294 patients analyzed the impact of OWT on TSH after 6 weeks of therapy. When compared to the SDT, patients of OWT had significantly higher serum TSH after 6 weeks of treatment [mean difference (MD) +1.85 mU/L (95% CI: 0.95–2.75 mU/L); \( P < 0.01; F = 63\% \) (moderate heterogeneity); Figure 3a; high certainty of evidence].

Data from only one study was available (Jayakumari 2019) evaluating the total T4 levels after 2 h of intake of thyroxine. In that study, total T4 levels were significantly higher after 2 h of thyroxine intake in people on OWT as compared to SDT [MD 3.05 mcg/dl (95% CI: 1.44–4.66 mcg/dl); \( P < 0.01; \) Figure 4b].

Data from only one study were available (Bornschein 2012) evaluating the total T4 levels after 4 h of intake of thyroxine. In that study total T4 levels was higher but not significantly different after 4 h of thyroxine intake in people on OWT as compared to SDT. [MD 2.70 mcg/dl (95% CI: -6.72–12.12 mcg/dl); \( P = 0.57; \) Figure 5b].

**Total T3**

Two studies with 219 patients analyzed the impact of OWT on serum total T3 after 6 weeks therapy. After 6 weeks of therapy, serum total T3 was not significantly different in people on OWT as compared to SDT [MD -0.87 mcg/dl (95% CI: -2.98–1.24 mcg/dl); \( P = 0.42; \) \( F = 65\% \) (moderate heterogeneity); Figure 3b; moderate certainty of evidence (MCE)].

Data from only one study was available (Jayakumari 2019) evaluating the total T4 levels after 2 h of intake of thyroxine. In that study, total T4 levels were significantly higher after 2 h of thyroxine intake in people on OWT as compared to SDT [MD 3.05 mcg/dl (95% CI: 1.44–4.66 mcg/dl); \( P < 0.01; \) Figure 4b].

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**Total T3**

Two studies with 219 patients analyzed the impact of OWT on serum total T3 after 6 weeks therapy. After 6 weeks of therapy, serum total T3 was significantly lower in people on OWT as compared to SDT. [MD -15.7 ng/dl (95% CI: -29.9–
Data from two studies with 80 patients was analyzed to evaluate the impact of thyroxine intake on free T4 levels after 2 h. Following 2 h of intake of thyroxine, serum free T4 was significantly higher in people on OWT as compared to SDT [MD 0.56 ng/dl (95% CI: 0.04–1.08 ng/dl); \( P = 0.03; F = 66\% \) (moderate heterogeneity); Figure 4d; MCE]. Data from only one study were available (Jayakumari 2019) evaluating the free T4 levels after 4 h of intake of thyroxine. In that study total T4 levels was significantly higher after 4 h of thyroxine intake in people on OWT as compared to SDT. [MD 0.70 ng/dl (95% CI: 0.52–0.88 ng/dl); \( P < 0.01; \) Figure 5a].

Free T3
Data from 1 study with 52 patients were analyzed to evaluate the impact of thyroxine intake on free T3 levels after 2 h. Following 2 h of intake of thyroxine, serum free T3 was lower but not significantly different after 4 h of thyroxine intake in people on OWT as compared to SDT. [MD -0.31 ng/dl (95% CI: -0.43–0.19 ng/dl); \( P = 0.43; \) Figure 5b].

Cardiac function parameters
Cardiac systolic function was assessed using echocardiography in different studies. Two commonly evaluated parameters were aortic ejection time (AET), isovolumetric contraction time (ICT), and left ventricular ejection fraction (LVEF). The findings suggest that OWT may have a positive effect on cardiac function compared to SDT.
time (ICT), and relation between AET and pre-ejection period (PEP) (AET/PEP ratio).

Data from two studies with 52 patients were analyzed to evaluate the impact on AET following 4–8 h of thyroxine intake. Following 4–8 h of intake of thyroxine, AET was lower but not significantly different in people on OWT as compared to SDT [MD -0.53 ms (95% CI: -1.38–0.99 ms); P = 0.22; I² = 0% (low heterogeneity); Figure 6a; MCE].

Data from two studies with 52 patients were analyzed to evaluate the impact on ICT following 4–8 h of thyroxine intake. Following 4–8 h of intake of thyroxine, ICT was significantly higher in people on OWT as compared to SDT [MD 3.62 ms (95% CI: 1.93–5.31 ms); P < 0.01; F = 0% (low heterogeneity); Figure 6b; MCE].

Data from two studies with 52 patients were analyzed to evaluate the impact on AET/PEP ratio following 4–8 h of thyroxine intake. Following 4–8 h of intake of thyroxine, AET/PEP ratio was significantly higher in people on OWT as compared to SDT [MD 0.01 (95% CI: 0.00–0.02); P = 0.02; F = 0% (low heterogeneity); Figure 6c; MCE].

Data from two studies with 52 patients were analyzed to evaluate the impact on HR following 4–8 h of thyroxine intake. Following 4–8 h of intake of thyroxine, HR ratio was not significantly different in people on OWT as compared to SDT [MD -0.89 (95% CI: -2.79–1.00); P = 0.36; F = 0% (low heterogeneity); Figure 6d; MCE].

Data from two studies with 76 patients were analyzed to evaluate the impact of the baseline on ICT following 4–8 h of thyroxine intake. Following 4–8 h of intake of thyroxine, ICT was not significantly different in people on OWT as compared to SDT [MD -0.01 (95% CI: -0.05–0.03); P = 0.63; Figure 7e]. Following 6 weeks of thyroxine therapy, HR was not significantly different in people on OWT as compared to SDT [MD -2.75 (95% CI: -8.38–2.88); P = 0.34; Figure 7e].

**DISCUSSION**

This meta-analysis showed that OWT as compared to SDT for thyroxine was associated with a small but statistically significant higher serum TSH and lower total T3 levels after 6 weeks of therapy, suggestive of less effective control of biochemical hypothyroidism. Following 2–4 h of thyroxine dose intake serum total T4, and free T4 were significantly higher in people on OWT as compared to SDT for hypothyroidism. Serum total T3 and free T3 were not significantly different following 2–4 h of thyroxine dose intake in people on OWT when compared to SDT. Among the cardiac echocardiographic parameters ICT and AET/PEP ratio were significantly higher following 2–4 h of thyroxine dose intake in people on OWT as compared to those on SDT. After 6 weeks of therapy, the cardiac echocardiographic parameters, HR, and occurrence of palpitations were not significantly different in people on OWT as compared to SDT.

Hence, our meta-analysis shows that OWT cannot replace the SDT for managing primary hypothyroidism in routine clinical practice.

**Figure 6:** Forest plot evaluating the impact of once weekly thyroxine (OWT) therapy as compared to standard daily therapy (SDT) on (a): Aortic ejection time (AET) at 4–8 h; (b): Isovolumetric contraction time (ICT) at 4–8 h; (c): AET/PEP ratio at 4–8 h; (d): Heart rate (HR) at 4–8 h.
Following dose administration of OWT, short-term echocardiographic changes may occur in some patients which does not persist following 6 weeks of therapy. Hence, OWT may be avoided in people with underlying cardiac disease. Also, the mild but significant increase in serum TSH with OWT as compared to SDT after 6 weeks therapy suggests that optimal control of biochemical hypothyroidism is less likely with OWT. Hence, only in special situations, where compliance might be an issue, and practical difficulties in implementing SDT, OWT may be tried with close periodic monitoring of thyroid function. In people who have worsening of thyroid function/symptomatology with OWT, it may be reasonable to switch back to the SDT for managing primary hypothyroidism. There is an urgent need for large multicentric RCTs with longer follow-up to more reasonably establish the long-term impact of OWT in managing primary hypothyroidism. There is also a need for long term cardiovascular safety data with the use of OWT for hypothyroidism.

There are several limitations associated with this meta-analysis. The absolute number of patients in this meta-analysis remains small, reflecting the scant work done on this topic in the last 4 decades. We were forced to include a non-RCT with 3 RCTs in this meta-analysis due to the scant data. However this reduces the quality of the meta-analysis. Three of the 4 studies in this meta-analysis were crossover trials which did not have washout phase, thereby having a high possibility of carryover effect which may have influenced the difference in hormone parameters between the study and control groups.

To conclude, it may be said that this first meta-analysis on the efficacy and safety of OWT as compared to SDT for managing primary hypothyroidism, suggests that OWT is associated with less efficient control of primary hypothyroidism at 6-weeks follow-up and may be associated with supraphysiologic elevation of thyroid hormone levels along with transient echocardiographic changes following 2-4 h of OWT dose intake in some of the patients.

Hence, OWT may not be the safest way to correct hypothyroidism, especially in elderly (for whom such a regimen was originally devised) with underlying cardiac disease.

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Conflicts of interest
There are no conflicts of interest.

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### Supplementary Table 1: Risk of bias assessment table of all the studies included in this meta-analysis

| Study            | Risk of Bias | Author Judgement                                                                 |
|------------------|--------------|----------------------------------------------------------------------------------|
| Bornschein 2012  | Low Risk     | Randomized Controlled Trial (RCT)                                                |
| Allocation       | Unclear Risk | Randomization Method not Present in the manuscript                                |
| Concealment (SB) |               |                                                                                  |
| Blinding         | Low Risk     | This was a cross-over study. Hence all participants received similar treatment over the 12 weeks. The nature of treatment were inter-changed at 6 weeks of follow-up |
| Of Participants & Personnel (P) | Low Risk | Single blinded study; the investigators were not aware of the patients in the study groups |
| Blinding         | Low Risk     |                                                                                  |
| Of Outcome       | Low Risk     |                                                                                  |
| Assessment (DB)  |               |                                                                                  |
| Incomplete       | Low Risk     | 14 patients were randomized and data from all the 14 patients were analysed at the end. Hence the attrition was 0%. |
| Outcome Data (AB) |               |                                                                                  |
| Reporting (RB)   | Low Risk     | All Pre-Specified Outcomes Were Reported                                          |
| Other Biases     | Low Risk     | Nothing Significant Noted                                                        |
| Grebe 1997       | Low Risk     | Randomized controlled trial                                                       |
| Allocation       | Unclear Risk | Randomization method not available in the manuscript                              |
| Concealment (SB) |               |                                                                                  |
| Blinding         | Low Risk     | This was a cross-over study. Hence all participants received similar treatment over the 12 weeks. The nature of treatment were inter-changed at 6 weeks of follow-up |
| Of Participants & Personnel (P) | Low Risk | Single blinded study; the investigators were not aware of the patients in the study groups |
| Blinding         | Unclear Risk | Blinding data not available                                                       |
| Of Outcome       | Low Risk     |                                                                                  |
| Assessment (DB)  |               |                                                                                  |
| Incomplete       | Low Risk     | 14 patients were included of which 12 patients completed the study                |
| Outcome Data (AB) |               |                                                                                  |
| Reporting (RB)   | Low Risk     | All Pre-Specified Outcomes Were Reported                                          |
| Other Biases     | Low Risk     | Nothing Significant Noted                                                        |
| Jayakumari 2019  | High Risk    | Not done; study participants were given the option to select once weekly thyroxine or daily thyroxine therapy |
| Allocation       | High Risk    | No allocation concealment done                                                    |
| Concealment (SB) |               |                                                                                  |
| Blinding         | High Risk    | Blinding not done; open labelled study                                            |
| Of Participants & Personnel (P) | High Risk | Open labelled study                                                             |
| Blinding         | High Risk    |                                                                                  |
| Of Outcome       | Low Risk     | Data from 52 patients were available for analysis from an initially included 54 patients. Hence attrition rate was only 3.7% |
| Assessment (DB)  |               |                                                                                  |
| Incomplete       | Low Risk     |                                                                                  |
| Outcome Data (AB) |               |                                                                                  |
| Reporting (RB)   | Low Risk     | All Pre-Specified Outcomes Were Reported                                          |
| Other Biases     | Low Risk     | Nothing significant noted                                                        |
| Rajput 2017      | Low Risk     | Randomized controlled trial (RCT); Method Of Randomization Reported; done using a random number table |
| Allocation       | Low Risk     | Randomization was achieved using a random number table. All investigators were blinded during the entire study |
| Concealment (SB) |               |                                                                                  |
| Blinding         | Low Risk     | This was a cross-over study. Hence all participants received similar treatment over the 12 weeks. The nature of treatment were inter-changed at 6 weeks of follow-up |
| Of Participants & Personnel (P) | Low Risk | Single blinded study; the investigators were not aware of the patients in the study groups |
| Blinding         | Low Risk     | All investigators were blinded during the entire study. They were not aware which patients were in which study group |
| Of Outcome       | Low Risk     |                                                                                  |
| Assessment (DB)  |               |                                                                                  |
| Incomplete       | Low Risk     | From the initially randomized 100 patients, data from 95 patients were analysed at the end of the study. Hence the attrition rate was only 5% |
| Outcome Data (AB) |               |                                                                                  |
| Reporting (RB)   | Low Risk     | All Pre-Specified Outcomes Were Reported                                          |
| Other Biases     | Low Risk     | Nothing significant noted                                                        |

### Supplementary Table 2: Risk of bias assessment of studies in this meta-analysis using Jadad Scale

| Study             | Randomization (0-2) | Blinding (0-2) | An account of all patients (0-1) | Total scoring (Quality)* |
|-------------------|---------------------|---------------|---------------------------------|--------------------------|
| Jayakumari et al., 2019 [11] | 0                   | 0             | 1                               | 1                        |
| Rajput et al., 2017 [10]   | 2                   | 0             | 0                               | 2                        |
| Bornschein et al., 2012 [4] | 2                   | 2             | 1                               | 5                        |
| Grebe et al., 1997 [5]     | 2                   | 0             | 0                               | 2                        |

*The thresholds for assessing quality as follows: 1) good (4-5 points); 2) fair (3 points); and 3) poor (0-2 points)