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 (FT4), 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); $P < 0.01$; $I^2 = 63\%$], comparable TT4 [MD -0.87 mcg/dl (95% CI: -2.98–1.24); $P = 0.42$; $I^2 = 65\%$], and significantly lower TT3 [MD -15.7 ng/dl (95% CI: -29.9–1.51); $P = 0.03$; $I^2 = 90\%$], 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); $P = 0.03$; $I^2 = 66\%$] were significantly higher 2 h after thyroxine intake, in people on OWT 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); $P < 0.01$; $I^2 = 0\%$] and aortic ejection time/pre-ejection period ratio [MD 0.01 (95% CI: 0.00–0.02); $P = 0.02$; $I^2 = 0\%$], 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

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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 not, whether the knowledge of the allocated

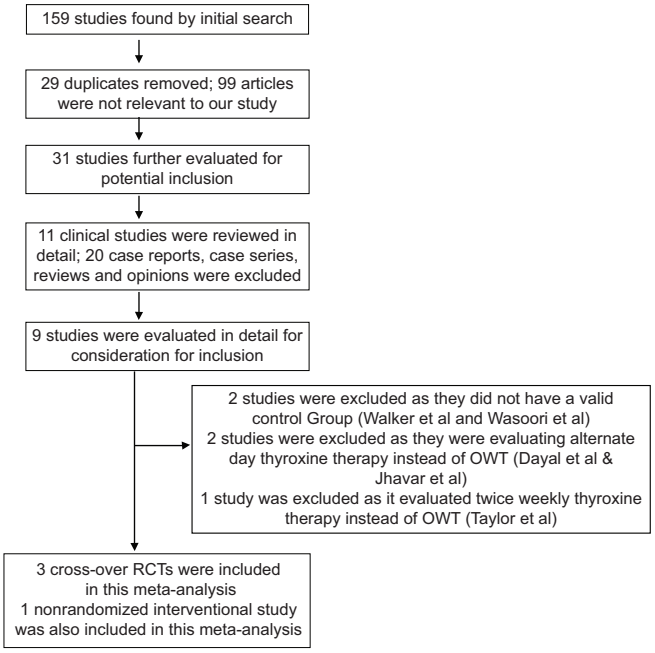

Figure 1: Flowchart elaborating on study retrieval and inclusion in the meta-analysis. RCT: randomized controlled trial; OWT: once weekly thyroxine therapy

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 >3 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 week 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
Age (years)				50.8±14.5
OWT:	33.2±9.3	35.4±8.4	42.5±7.48	(NA group-wise)
SDT:	35.61±12.7	36.1±10.7	41.2±8.41	
Weight (kg)			NA	NA
OWT:	61.95±16.2	64.5±9.0		
SDT:	63.11±14.6	64.4±10.1		
BMI (kg/m2)			NA	NA
OWT:	25.03±5.4	26.1±3.0		
SDT:	29.63±6.6	26.4±3.8		
Pulse Rate, beats/min				NA
OWT:	76±6.2	77.8±7.2	87.5±7.3	
SDT:	74±6.3	77.5±8.4	79.2±11.1	
Duration of hypothyroidism (yrs)		NA	NA	NA
OWT:	11.2±8.0			
SDT:	11.1±7.2			
TSH (mIU/L)				NA
OWT:	31.3 (17.5 – 53.2)	2.6±1.4	2.38±1.37	
SDT:	36.5 (23.8 – 53.3)	2.5±1.4	2.39±1.19	
TT4 (mcg/dl)			NA	NA
OWT:	7.5±2.9	9.3±1.2		
SDT:	8.8±7.43	8.9±1.5		
fT4 (ng/dl)	NA	NA		NA
OWT:			1.13±0.15	
SDT:			1.12±0.17	
Dose of LT4 given (mcg/kg/day)		NA		1.6±0.35
OWT:	1.8±0.7		1.22±0.08	(NA group-wise)
SDT:	2.31±0.03		1.11±0.14	

HSS: Hyperthyroid symptom score. *Systolic function was analyzed by: preejection period (PEP), aortic ejection time (ET), isovolumetric contraction time (ICT), and heart rate (HR)

Table 2: Baseline characteristics of excluded studies

Author, year (ref)	Jhavar *et al*., 2018[10]	Wasoori *et al*., 2017[11]	Dayal *et al*., 2013[12]	Walker *et al*., 2013[13]	Taylor *et al*., 1994[14]
Study design	Prospective interventional study	Randomized prospective observational study	Prospective case control study	Prospective interventional study	Randomized crossover study
Participants	Subclinical hypothyroidism, aged 18-45 years	Hypothyroid patients, aged 18-55 years; 3 groups- G1-TSH≤4.2 mIU/L, G2-TSH>4.2 mIU/L, G3-newly diagnosed hypothyroid with TSH>4.2 mIU/L	Children with congenital hypothyroidism, age>4 years, euthyroid for 6 months prior	Primary hypothyroid, not controlled (TSH>5.5 mIU/L) despite adequate LT4 dose (≥ 1.6 mcg/kg/d)	Hypothyroid patients, aged 73-95 years
Duration	3 months	24 weeks	3 months	4 weeks	2 phases- each of 4 weeks duration
Intervention	50 mcg LT4, on alternate days	Once weekly LT4, with seven times the previous daily dose	Alternate day LT4, double of previous daily dose	Once weekly LT4, with seven times the previous daily dose	Twice weekly LT4 (calculated to give seven times the previous daily dose)
Control	None	None	Continue previous daily LT4 dose	None	Continue previous LT4 dose
N	50	180 (60 in each group)	70 (40 intervention/30 control)	23	7
Outcomes measured	TSH, T4, T3, BMI, BP, Cholesterol, TG	TSH, T3, T4, thyroid symptoms	TSH, TT3, TT4, thyroid symptoms, AST, ALT, lipids	TSH, fT4, thyroid symptoms	TSH, T3, T4, fT4, systolic time interval
Remarks	Used alternate day LT4 in subclinical hypothyroidism, no control group	Once weekly LT4 compared within 3 groups, no control group with daily LT4 therapy	Compared alternate day LT4 with daily therapy in congenital hypothyroidism	Used once weekly LT4, No control group	Twice weekly LT4 compared with daily therapy in elderly patients

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.[8] 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 Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test.[15] 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 Chi^2 test, or a confidence interval for I^2).[15]

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.[15] 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 an 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.,*[4] Grebe *et al.,*[5] Rajput *et al.*[9]), and one non RCT Jayakumari *et al.,*[8] 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

Summary of findings:

Weekly thyroxine compared to daily thyroxine in managing primary hypothyroidism

Patient or population: managing primary hypothyroidism
Setting:
Intervention: Weekly thyroxine
Comparison: Daily thyroxine

Outcomes	Anticipated absolute effects (95% CI)		№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with daily thyroxine	Risk with weekly thyroxine		
TSH (thyroid stimulating hormone) (6 weeks)	The mean TSH (thyroid stimulating hormone) (6 weeks) was 8.52 mU/L	MD 1.85 mU/L higher (0.95 higher to 2.75 higher)	294 (4 RCTs)	⊕⊕⊕⊕ HIGH
Total T4 (6 weeks)	The mean total T4 (6 weeks) was 8.56 mcg/dl	MD 0.87 mcg/dl lower (2.98 lower to 1.24 higher)	242 (2 RCTs)	⊕⊕⊕◯ MODERATE [a]
Total T3 (6 weeks)	The mean total T3 (6 weeks) was 121.95 ng/dl	MD 15.7 ng/dl lower (29.9 lower to 1.51 lower)	218 (2 RCTs)	⊕⊕⊕◯ MODERATE [a]
Total T4 (2 h)	The mean total T4 (2 h) was 8.24 mcg/dl	MD 3.05 mcg/dl higher (1.44 higher to 4.66 higher)	52 (1 RCT)	⊕⊕⊕◯ MODERATE [a]
Total T3 (2 h)	The mean total T3 (2 h) was 101.8 ng/dl	MD 3.79 ng/dl higher (4.53 lower to 12.11 higher)	80 (2 RCTs)	⊕⊕⊕◯ MODERATE [a]
Free T4 (4 h)	The mean free T4 (4 h) was 1.385 ng/dl	MD 0.7 ng/dl higher (0.52 higher to 0.88 higher)	52 (2 RCTs)	⊕⊕⊕◯ MODERATE [a]
Aortic Ejection Time (4-8 h)	The mean aortic Ejection Time (4-8 h) was 371 ms	MD 6.41 ms lower (13.8 lower to 0.99 higher)	52 (2 RCTs)	⊕⊕⊕◯ MODERATE [a]
Isovolumetric Contraction Time (4-8 h)	The mean isovolumetric Contraction Time (4-8 h) was 47.35 ms	MD 3.62 ms higher (1.93 higher to 5.31 higher)	52 (2 RCTs)	⊕⊕⊕◯ MODERATE [a]
AET/PEP (4-8 h)	The mean AET/PEP (4-8 h) was 0.276	MD 0.01 higher (0 to 0.02 higher)	52 (2 RCTs)	⊕⊕⊕◯ MODERATE [a]

[a]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); $P < 0.01$; $I^2 = 63\%$ (moderate heterogeneity); Figure 3a; high certainty of evidence].

Effect of once weekly thyroxine on secondary outcomes

Total T4

Two studies with 242 patients analyzed the impact of OWT on serum total T4 after 6 weeks therapy. After 6 weeks of therapy, serum total T4 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); $P = 0.42$; I^2 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]. 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 significantly lower in people on OWT as compared to SDT. [MD -15.7 ng/dl (95% CI: -29.9–

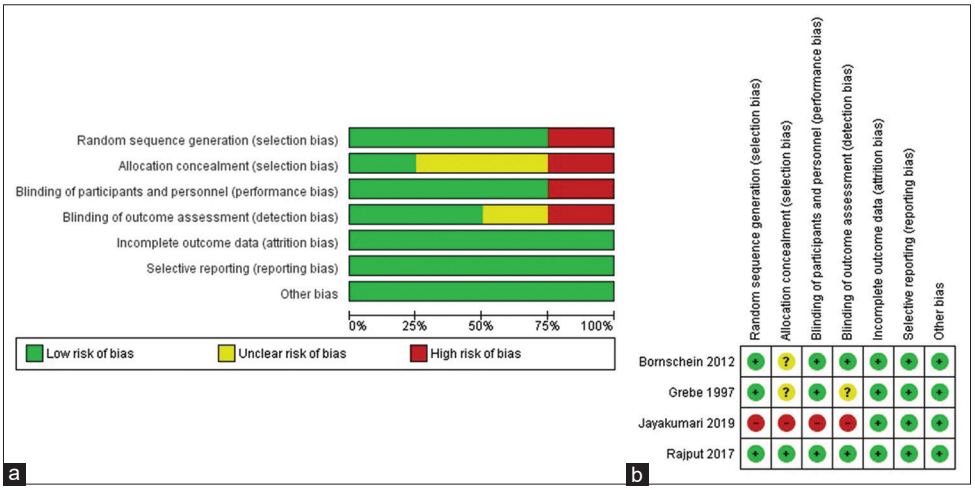

Figure 2: (a). Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies; (b). Risk of bias summary: review authors' judgements about each risk of bias item for each included study

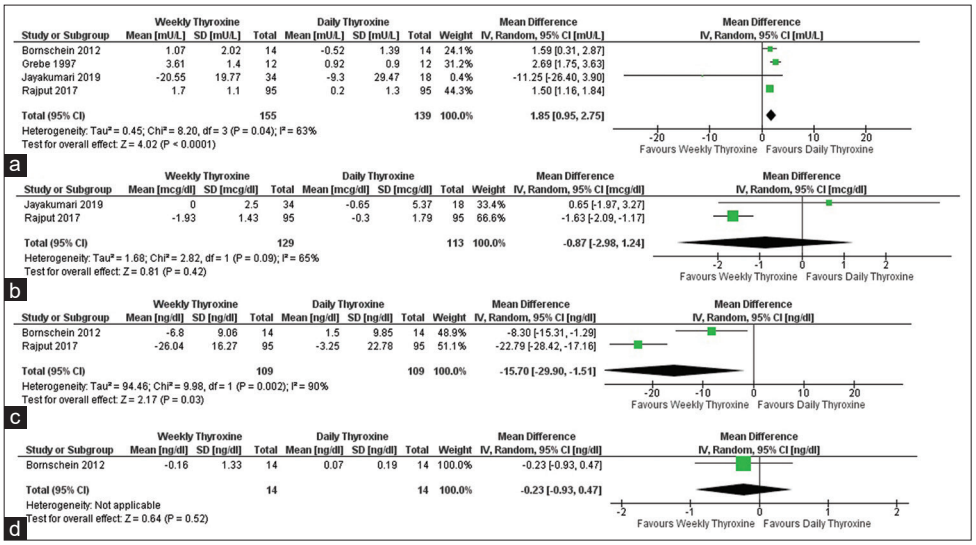

Figure 3: Forest plot evaluating the impact of once weekly thyroxine (OWT) therapy as compared to standard daily therapy (SDT) on (a) TSH at 6 weeks; (b): Total T4 at 6 weeks; (c) Total T3 at 6 weeks; (d): Free T4 at 6 weeks

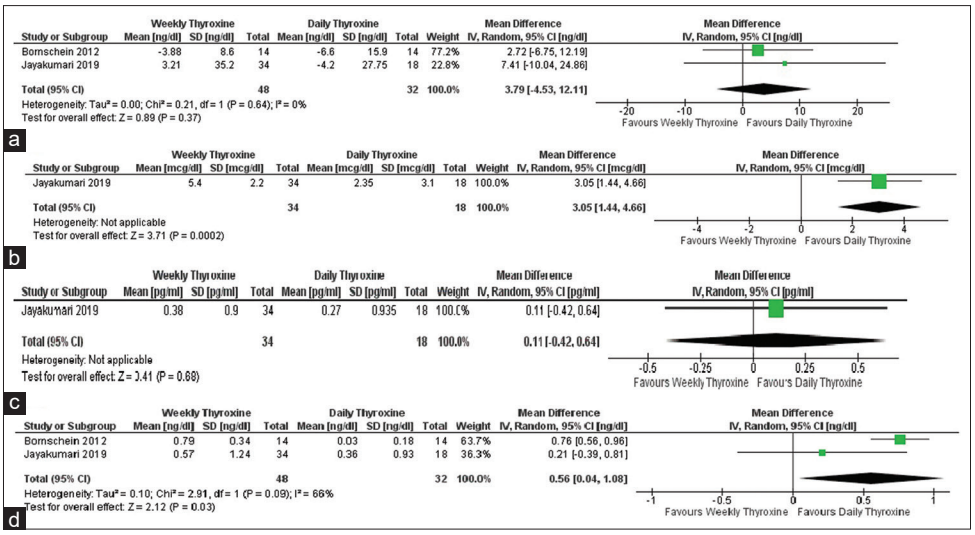

Figure 4: Forest plot evaluating the impact of once weekly thyroxine (OWT) therapy as compared to standard daily therapy (SDT) on (a): Total T3 at 2 h; (b): Total T4 at 2 h; (c): Free T3 at 2 h; (d): Free T4 at 2 h

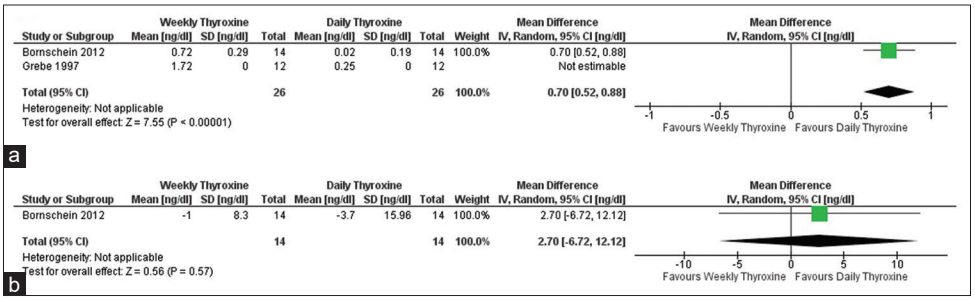

Figure 5: Forest plot evaluating the impact of once weekly thyroxine (OWT) therapy as compared to standard daily therapy (SDT) on (a): Free T4 at 4 h; (b): Total T3 at 4 h

1.51 ng/dl); $P = 0.03$; $I^2 = 90\%$ (high heterogeneity); Figure 3c; MCE].

Data from two studies with 80 patients were analyzed to evaluate the impact of thyroxine intake on total T3 levels after 2 h. Following 2 h of intake of thyroxine, serum total T3 was not significantly different in people on OWT as compared to SDT [MD 3.79 ng/dl (95% CI: -4.53–12.11 ng/dl); $P = 0.37$; $I^2 = 0\%$ (low heterogeneity); Figure 4a; MCE]. Data from only one study were available (Bornschein, 2012) evaluating the total T3 levels after 4 h of intake of thyroxine. In that study total T3 levels was not significantly different after 4 h of thyroxine intake in people on OWT as compared to SDT. [MD 2.70 ng/dl (95% CI: -6.72–12.12 ng/dl); $P = 0.57$].

Free T4

Data from only one study were available (Bornschein 2012) evaluating the free T4 levels after 6 weeks of intake of thyroxine. In that study, free T4 levels was not significantly different after 6 weeks of thyroxine intake in people on OWT as compared to SDT. [MD -0.23 ng/dl (95% CI: -0.93–0.47 ng/dl); $P = 0.52$; Figure 3d].

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); $P = 0.03$; $I^2 = 66\%$ (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 in people on OWT as compared to SDT [MD 0.11 pg/ml (95% CI: -0.42–0.64 pg/ml); $P = 0.68$; Figure 4c; MCE].

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 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 -6.41 ms (95% CI: -13.8–0.99 ms); $P = 0.09$; $I^2 = 0\%$ (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); $P < 0.01$; $I^2 = 0\%$ (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); $P = 0.02$; $I^2 = 0\%$ (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); $P = 0.36$; $I^2 = 0\%$ (low heterogeneity); Figure 6d; MCE].

Data from two studies with 76 patients were analyzed to evaluate the impact of thyroxine intake on patient reported palpitations following 6 weeks of therapy. Following 6 weeks of thyroxine therapy, patient reported palpitations were not significantly different in people on OWT as compared to SDT [MD 1.13 (95% CI: 0.23–5.64); $P = 0.88$; $I^2 = 0\%$ (low heterogeneity); Figure 7a; MCE].

Data from only one study were available (Bornschein, 2012) evaluating echocardiographic cardiac parameters following 6 weeks of thyroxine therapy. Following 6 weeks of thyroxine therapy, AET was not significantly different in people on OWT as compared to SDT [MD -4 ms (95% CI: -24.8–16.8 ms); $P = 0.71$; Figure 7b]. Following 6 weeks of thyroxine therapy, ICT was not significantly different in people on OWT as compared to SDT [MD -3.94 ms (95% CI: -17.28–9.4 ms); $P = 0.56$; Figure 7c]. Following 6 weeks of thyroxine therapy, AET/PEP ratio 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 7d]. 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 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

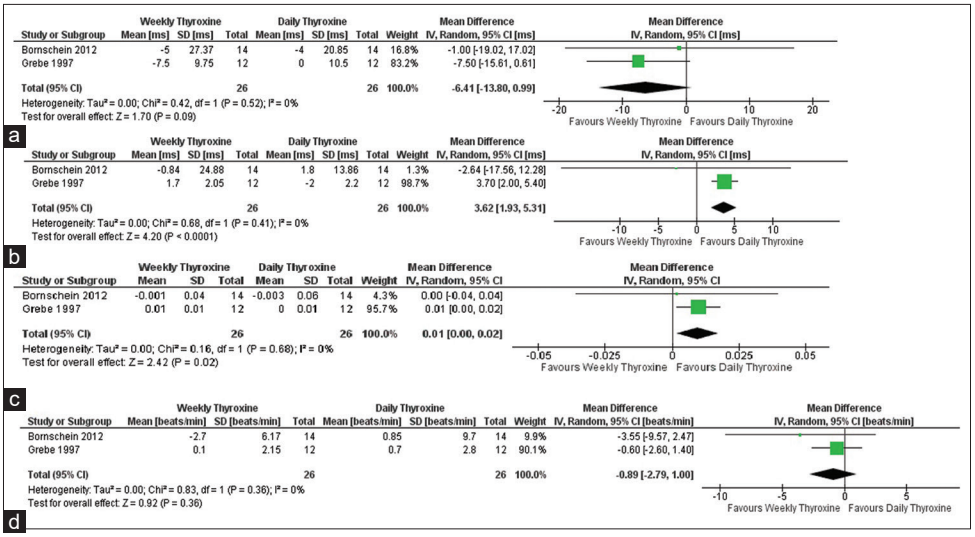

Figure 6: Forest plot evaluating the impact of once weekly thyroxine (OWT) therapy as compared to standard daily therapy (SDT) on (a): Aortic ejection time (AET) at 4-8 h; (b): Isovolumetric contraction time (ICT) at 4-8 h; (c): AET/PEP ratio at 4-8 h; (d): Heart rate (HR) at 4-8 h

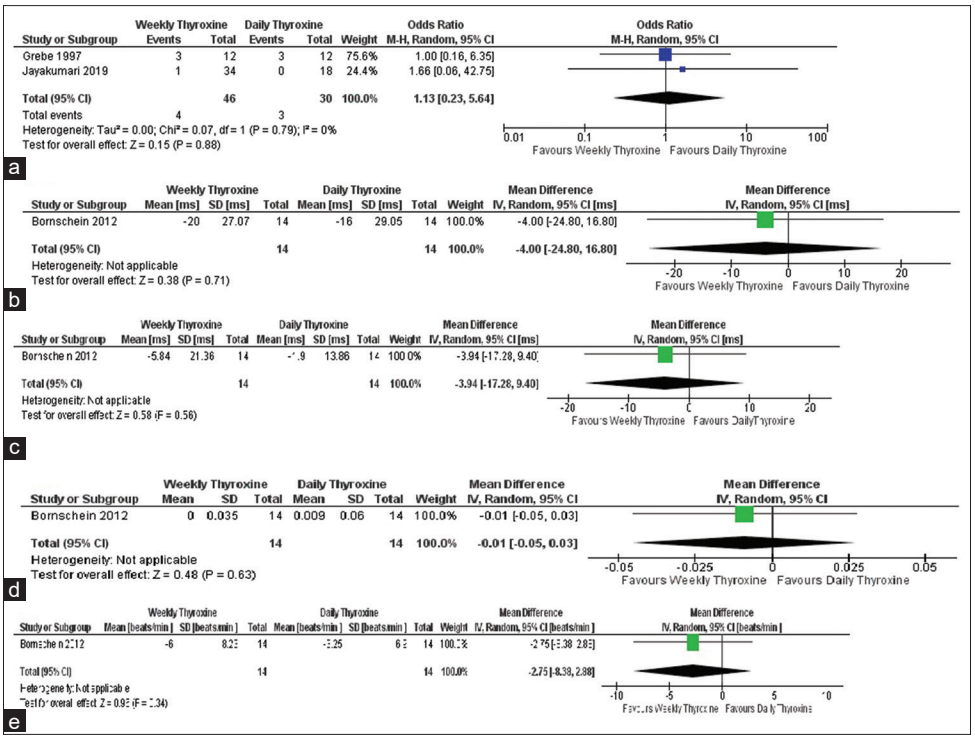

Figure 7: Forest plot evaluating the impact of once weekly thyroxine (OWT) therapy as compared to standard daily therapy (SDT) on (a): palpitations at 6 weeks; (b): aortic ejection time (AET) at 6 weeks; (c): isovolumetric contraction time (ICT) at 6 weeks; (d): AET/PEP ratio at 6 weeks; (e): heart rate (HR) at 6 weeks

practice. 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 if 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.

References

1. Kumar P, Khandelwal D, Mittal S, Dutta D, Kalra S, Katiyar P, *et al*. Knowledge, awareness, practices and adherence to treatment of patients with primary hypothyroidism in Delhi. Indian J Endocrinol Metab 2017;21:429-33.
2. Dutta D, Garg A, Khandelwal D, Kalra S, Mittal S, Chittawar S. Thyroid symptomatology across the spectrum of hypothyroidism and impact of levothyroxine supplementation in patients with severe primary hypothyroidism. Indian J Endocrinol Metab 2019;23:373-8.
3. Surana V, Aggarwal S, Khandelwal D, Singla R, Bhattacharya S, Chittawar S, *et al*. A 2016 clinical practice pattern in the management of primary hypothyroidism among doctors from different clinical

specialties in New Delhi. Indian J Endocrinol Metab 2017;21:165-77.
4. Bornschein A, Filho GP, Graf H, Gisah A, Carvalh D. Treating primary hypothyroidism with weekly doses of levothyroxine: A randomized, single-blind, crossover study. Arq Bras Endocrinol Metab 2012;56:250-8.
5. Grebe SKG, Cooke RR, Ford HC, Fagerstr¨om JN, Cordwell DP, Lever NA, *et al*. Treatment of hypothyroidism with once weekly thyroxine. J Clin Endocrinol Metab 1997;82:870-5.
6. Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, Celi FS, *et al*. Guidelines for the treatment of hypothyroidism: Prepared by the American Thyroid Association task force on thyroid hormone replacement. Thyroid 2014;24:1670–751.
7. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, *et al*. The PRISMA statement for reporting systematic reviews and metaanalyses of studies that evaluate healthcare interventions: Explanation and elaboration. BMJ 2009;339:b2700.
8. Clark HD, *et al*. Assessing the quality of randomized trials: reliability of the Jadad scale. Control Clin. Trials 1999;20:448-52.
9. Rajput R, Pathak V. The effect of daily versus weekly levothyroxine replacement on thyroid function test in hypothyroid patients at a tertiary care centre in Haryana. Eur Thyroid J 2017;6:250-4.
10. Jhavar D, Naredi M. A study of subclinical hypothyroidism treated with alternate day fixed dose thyroxine therapy. Int J Adv Med 2018;5:658-62.
11. Wasoori S, Naik M, Pande D, Bhardwaj C. Hypothyroidism - once a week treatment option in young and middle aged adults. Endocr Pract 2017;23(Suppl 3):252.
12. Dayal D, Saini L, Attri SV, Singh B, Bhalla AK. Daily versus alternate day thyroxine therapy to maintain euthyroidism in children with congenital hypothyroidism. Int J Endocrinol Metab 2013;11:e9499. doi: 10.5812/ijem. 9499.
13. Walker JN, Shillo P, Ibbotson V, Vincent A, Karavitaki N, Weetman AP, *et al*. A thyroxine absorption test followed by weekly thyroxine administration: A method to assess non-adherence to treatment. Eur J Endocrinol 2013;168:913-7.
14. Taylor J, Williams BO, Frater J, Stott DJ, Connell J. Twice-weekly dosing for thyroxine replacement in elderly patients with primary hypothyroidism. J Int Med Res 1994;22:273-7.
15. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, *et al*. GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-6.
16. Song F, Eastwood AJ, Gilbody S, Duley L, Sutton AJ. Publication and related biases. Health Technol Assess 2000;4:1-115.

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

Bornschein 2012	Risk of Bias	Author Judgement
Random Sequence Generation (Selection Bias)	Low Risk	Randomized Controlled Trial (RCT)
Allocation Concealment (Selection Bias)	Unclear Risk	Randomization Method not Present In The Manuscript
Blinding Of Participants & Personel (Performance Bias)	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 6weeks of follow-up
Blinding Of Outcome Assessment (Detection Bias)	Low Risk	Single blinded study; the investigators were not aware of the patients in the study groups
Incomplete Outcome Data (Attrition Bias)	Low Risk	14 patients were randomized and data from all the 14 patients were analysed at the end. Hence the attrition was 0%.
Selective Reporting (Reporting Bias)	Low Risk	All Pre-Specified Outcomes Were Reported
Other Biases	Low Risk	Nothing Significant Noted
Grebe 1997	**Risk of Bias**	**Author Judgement**
Random Sequence Generation (Selection Bias)	Low Risk	Randomized controlled trial
Allocation Concealment (Selection Bias)	Unclear Risk	Randomization method not available in the manuscript
Blinding Of Participants & Personel (Performance Bias)	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 6weeks of follow-up
Blinding Of Outcome Assessment (Detection Bias)	Unclear Risk	Blinding data not available
Incomplete Outcome Data (Attrition Bias)	Low Risk	14 patients were included of which 12 patients completed the study
Selective Reporting (Reporting Bias)	Low Risk	All Pre-Specified Outcomes Were Reported
Other Biases	Low Risk	Nothing Significant Noted
Jayakumari 2019	**Risk of Bias**	**Author Judgement**
Random Sequence Generation (Selection Bias)	High Risk	Not done; study participants were given the option to select once weekly thyroxine or daily thyroxine therapy
Allocation Concealment (Selection Bias)	High risk	No allocation concealment done
Blinding Of Participants & Personel (Performance Bias)	High Risk	Blinding not done; open labelled study
Blinding Of Outcome Assessment (Detection Bias)	High Risk	Open labelled study
Incomplete Outcome Data (Attrition Bias)	Low Risk	Data from 52 patients were available for analysis from an initially included 54 patients. Hence attrition rate was only 3.7%
Selective Reporting (Reporting Bias)	Low Risk	All Pre-Specified Outcomes Were Reported
Other Biases	Low Risk	Nothing significant noted
Rajput 2017	**Risk of Bias**	**Author Judgement**
Random Sequence Generation (Selection Bias)	Low Risk	Randomized controlled trial (RCT); Method Of Randomization Reported; done using a random number table
Allocation Concealment (Selection Bias)	Low Risk	Randomization was achieved using a random number table. All investigators were blinded during the entire study
Blinding Of Participants & Personel (Performance Bias)	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 6weeks of follow-up
Blinding Of Outcome Assessment (Detection Bias)	Low Risk	All investigators were blinded during the entire study. They were not aware which patients were in which study group
Incomplete Outcome Data (Attrition Bias)	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%.
Selective Reporting (Reporting Bias)	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)