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Age-Related Serum Thyroid-Stimulating Hormone Reference Range in Older Patients Treated with Levothyroxine: A Randomized Controlled Feasibility Trial (SORTED 1)

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Keywords
Thyroid-stimulating hormone · Hypothyroidism · Reference range · Levothyroxine · Elderly

Abstract
Introduction: Serum thyroid-stimulating hormone (TSH) increases with age but target TSH is similar in younger and older hypothyroid patients on treatment. It is unknown if quality of life (QoL), hypothyroid symptoms and cardiovascular risk factors change in older hypothyroid patients treated to an age-appropriate reference range. ***Objective:*** To assess if a higher target serum TSH of 4.01–8.0 mU/L is feasible in, and acceptable to, older treated hypothyroid patients. ***Methods:*** A single-blind (participant) randomised controlled feasibility trial involving 48 hypothyroid patients aged ≥80 years on established and stable levothyroxine (LT4) therapy with serum TSH levels within the standard reference range (0.4–4.0 mU/L) was conducted. Standard (0.4–4.0 mU/L) or higher (4.1–8.0 mU/L) TSH target (standard TSH [ST] or higher TSH [HT] groups) LT4 for 24 weeks was administered. The outcome measures evaluated were thyroid function tests, QoL, hypothyroid symptoms, cardiovascular risk factors and serum marker of bone resorption in participants that completed the trial (n = 21/24 ST group, n = 19/24 HT group). ***Results:*** At 24 weeks, in the ST and HT groups, respectively, median (interquartile range) serum TSH was 1.25 (0.76–1.72) and 5.50 (4.05–9.12) mU/L, mean (± SD) free thyroxine (FT4) was 19.4 ± 3.5 and 15.9 ± 2.4 pmol/L, and daily LT4 dose was 82.1 ± 26.4 and 59.2 ± 23.9 µg. There was no suggestion of adverse impact of a higher serum TSH in the HT group with regard to any of the outcomes assessed. ***Conclusions:*** In hypothyroid patients aged ≥80 years on LT4 therapy for 24 weeks, there was no evidence that a higher target serum TSH was associated with an adverse impact on patient reported outcomes, cardiovascular risk factors or bone resorption marker over 24 weeks. Longer-term trials assessing morbidity and mortality outcomes and health-utility in this age group are feasible and should be performed.

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Background

Worldwide, there has been an increase in human lifespan and reduction in early mortality. These 2 factors and the associated reduction in the number of childbirths have led to an increase in the proportion of older people. The fastest population increase has been in the number of those aged 85 and over – the "oldest old." For instance, in the United Kingdom, there were around 660,000 people aged 85 and over in 1984. Since then the numbers have more than doubled reaching 1.5 million in 2015 [1]. By 2034, the number of people aged 85 and over is projected to reach 3.5 million and account for 5% of the total population [2]. Similar trends are being observed in almost all developed nations including the United States [3].

Hypothyroidism has a prevalence of up to 16% in elderly females and the number of individuals diagnosed with it is expected to rise due to increased life expectancy [4–7]. Currently, all individuals with hypothyroidism are treated as a homogenous group irrespective of age to aim for serum thyroid-stimulating Hormone (TSH) levels within the population reference range (generally in the range of 0.4–4.0 mU/L) [8]. But, thyroxine metabolism is altered in advanced age, and "age-adjusted" reference ranges are not employed [9]. In older untreated individuals, the upper limit of TSH is 7.5 mU/L as opposed to 4.0 mU/L in the younger age groups [4]. Several meta-analyses of observational population-based studies have confirmed that mild hypothyroidism left untreated in the elderly is not hazardous for vascular mortality and events [10–12]. Furthermore, slightly high TSH levels in the very old (>85 years) have been shown to be associated with either better survival [13] or no unfavourable outcomes [14]. Moreover, a proportion of treated hypothyroid individuals may have adverse effects due to inadvertent over-treatment (such as osteoporosis and atrial fibrillation) [15]. In addition, treatment of subclinical hypothyroidism, by far the commonest form of the disease, in older individuals may not be associated with the same cardiovascular benefit as that observed in younger patients [16]. Thus, treating older individuals with lower doses of levothyroxine (LT4) with the aim to keep serum TSH levels at a slightly higher level may be more physiological, not cause any harm, and may even be beneficial. Some experts have suggested that older hypothyroid individuals' LT4 treatment should be tailored to have a higher target TSH value compared to younger individuals and that "prospective therapeutic trials are necessary to clarify the necessity of replacement therapy in the elderly" [17]. However, no high-grade evidence exists to be able to guide clinical practice in this area. Hence, it is imperative to determine whether older individuals should have age-appropriate TSH target therapy, and whether this is safe and does not impair quality of life (QoL). Currently, it is unknown whether a lower dose of LT4, aiming for a slightly higher serum TSH target, is associated with any changes in patient reported outcomes. We therefore performed a randomised controlled feasibility trial with the primary aim to assess participants' willingness to enter the trial and acceptability of trial design; the results have been published elsewhere [18]. Here we report the impact of a higher serum TSH target in older LT4-treated hypothyroid patients on the secondary outcomes from the feasibility trial: QoL, symptoms, and cardiovascular risk factors and bone risk marker.

Methods

Participants

The trial was conducted across the Northumberland, Tyne and Wear area in the North East of England and the protocol has been described previously [19]. Participants who were eligible to participate in the study were identified and invited from 20 Primary Care Centres in 2012. The inclusion criteria were as follows: patients aged 80 years or older, diagnosed with hypothyroidism and treated with LT4 for at least 6 months, living independently in the community and serum TSH of 0.4–4.0 mU/L within the last 3 months prior to and at the point of participating in the study. The exclusion criteria were as follows: those with dementia and other conditions in whom informed consent could not be provided, nursing home or care home residents, those with thyroid cancer requiring suppressive doses of LT4 and those on 25 μg of LT4 daily as reducing their dose would mean stopping treatment completely (the minimum dose of LT4 available in the United Kingdom is 25 μg). All participants provided written informed consent and ethical approval was obtained from the relevant research Ethics Committee. The trial was registered on the Clinical Trials databases (ISRCTN number 16043724, Clinical Trials.gov NCT01647750).

Trial design, recruitment and intervention: This was a dual-centre, single-blind (participant level) parallel randomised controlled trial as part of a feasibility study for conducting a subsequent larger multicentre trial. Participants were randomly allocated to once daily LT4 therapy in 1:1 ratio aiming for either standard TSH (ST arm) target (range 0.4–4.0 mU/L) or a higher TSH (HT arm) target (range 4.1–8.0 mU/L), using permuted blocks within strata. Randomisation was stratified according to pre-study LT4 dose (50, 75, 100, and 125 μg or more daily). The research team performed the randomisations using a secure password-protected web-based system.

Participants were recruited from November 2012 till July 2013 and the final patient completed the study related visit in January 2014. Participants were studied either at a hospital-based Clinical Research Facility or out-patient departments, or the participants' homes, depending on participants' preference.

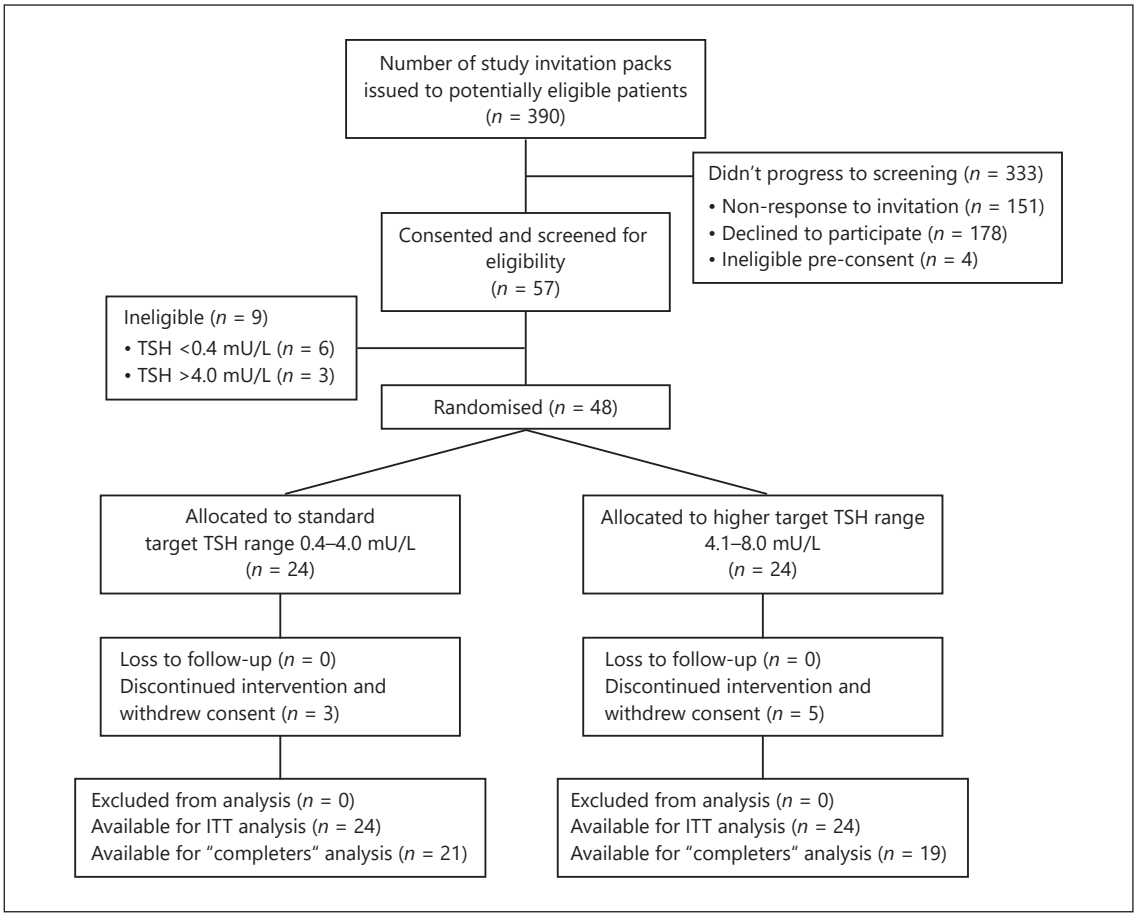

Fig. 1. Consort flowchart of the progress of patients through the trial. TSH, thyroid-stimulating hormone.

The study drug (LT4) was over-encapsulated to maintain participant-level blinding and participants were provided with written instructions to take one capsule daily. At baseline (visit 1), participants randomised to the ST arm were prescribed one capsule containing their usual (pre-study) dose of LT4, whereas those randomised to the HT arm were given capsules containing 25 μg less than their pre-study daily LT4 dose. At visit 2 (at 12 weeks), the dose of the LT4 was adjusted, based on the target TSH level aimed for in the respective groups. Treatment compliance was assessed by capsule compliance at the end of each study visit (weeks 12 and 24).

Assessments

Patient-Reported Outcomes

Assessments were performed at baseline and at the end of the trial at 24 weeks. General health and well-being was measured by utilising the widely used generic questionnaire European five-dimensional QoL (EQ-5D) 3 L. It is the instrument recommended by NICE for evidence submitted to its technology appraisal process [20]. The visual analogue scale of the EQ-5D was used to assess participants' overall health on a vertical scale ranging from "worst possible" (classed as 0) to "best possible" (classed as 100).

Hypothyroid dependent- QoL was assessed using a validated tool, the hypothyroid-dependent QoL (ThyDQoL) [21, 22]. Hypothyroid dependent QoL is evaluated by the average weighted impact (AWI) score obtained by summing all applicable weighted domain scores, before dividing by the number of domains applicable to the individual. The ThyDQoL AWI scores range from –9 to +3 (maximum negative to maximum positive weighted impact of hypothyroidism on the average of all applicable domains). Hypothyroid symptoms were evaluated by a validated measure, the ThySRQ that assesses the presence of symptoms of hypothyroidism [23]. The ThySRQ enquires about 15 symptoms of hypothyroidism including tiredness, weight gain, feeing cold, memory problems and feeling depressed. The full list of 15 symptoms and the psychometric properties of the ThySRQ have previously been published [23]. For reasons of brevity, only the 4 most frequent symptoms are reported in this analysis.

Falls Risk Assessment

The falls risk assessment tool [24] and Timed up and go test [25] are fast, easy-to-apply and validated measures for screening the risk of falls among elderly individuals. The falls risk assessment tool assesses the risk of falls and is scored from 5 (lowest risk) to 20 (highest risk). The Timed up and go test evaluates mobility as well as balance and a score of 14 s or more indicates a high risk of falls.

Table 1. Baseline characteristics for the ITT (n = 48) and the completers (n = 40) analysis sets, by randomised treatment group

	ITT analysis set (n = 48)		Completers analysis set (n = 40)	
	standard TSH target range (n = 24)	higher TSH target range (n = 24)	standard TSH target range (n = 21)	higher TSH target range (n = 19)
Gender, female, n (%)	18 (75)	16 (67)	16 (76)	13 (68)
Age, years, mean ± SD	84.4±3.5	84.4±3.6	83.9±3.1	84.0±3.3
Other medical conditions, n (%)				
Type 2 diabetes mellitus	2 (8.3)	2 (8.3)	2 (9.5)	2 (10.5)
Ischaemic heart disease	6 (25)	7 (29.2)	5 (23.8)	7 (36.8)
Cerebrovascular disease	4 (16.7	3 (12.5)	2 (9.5)	3 (15.8)
Hypertension	13 (54.2)	11 (45.8)	10 (47.6)	9 (47.4)
COPD	2 (8.3)	4 (16.7)	1 (4.8)	4 (21.1)
Anxiety/depression	4 (16.7)	8 (33.3)	3 (14.3)	7 (36.8)
Blood pressure, mm Hg, mean ± SD				
Systolic	162.0±25.7	154.3±22.8	161.3±24.9	148.9±20.2
Diastolic	86.6±14.0	84.0±10.9	86.2±14.6	83.6±11.8
Physical examination, mean ± SD				
Weight, kg	68.7±13.2	68.3±13.3	70.1±13.5	68.1±13.6
BMI, kg/m^2	27.1±4.8	27.2±4.6	27.5±5.0	27.5±4.9
Pulse, bpm	67.8±9.9	68.1±10.0	66.9±9.8	66.6±9.4
Blood results, mean ± SD				
TSH, mU/L	1.34±0.81	2.00±1.05	1.37±0.85	2.00±1.05
FT3, pmol/L	3.88±0.37	3.73±0.48	3.86±0.39	3.73±0.48
FT4, pmol/L*	18.87±2.59	18.12±2.31	18.74±2.68	18.16±2.04
FT3:FT4 ratio*	0.21±0.04	0.21±0.03	0.21±0.04	0.21±0.03
Total cholesterol, mmol/L	5.18±1.40	5.12±1.11	5.09±1.43	5.14±1.14
HDL cholesterol, mmol/L	1.68±0.50	1.65±0.36	1.64±0.52	1.67±0.36
Triglycerides, mmol/L	1.58±0.85	1.45±0.58	1.68±0.86	1.48±0.63
Serum CTx, pg/mL	0.30±0.19	0.34±0.24	0.30±0.20	0.37±0.25
TPO antibodies, n (%)				
<35 IU/mL	12 (50)	16 (67)	9 (43)	13 (68)
≥35 IU/mL	12 (50)	8 (33)	12 (57)	6 (32)
QoL/symptoms				
EQ-5D VAS, mean ± SD	69.1±18.5	75.0±14.3	69.0±17.4	74.9±15.6
ThyDQoL (AWI-18), mean ± SD	–0.45±0.86	–0.46±0.88	–0.37±0.68	–0.42±0.69
Tired recently, n (%)	19 (79)	17 (71)	17 (81)	14 (74)
Recent memory problems, n (%)	12 (52)	14 (58)	11 (52)	11 (58)
Dry skin, n (%)	13 (54)	13 (54)	11 (52)	10 (53)
Feeling the cold, n (%)	10 (42)	15 (63)	9 (43)	14 (74)
Depressed recently, n (%)	7 (30)	8 (33)	6 (29)	5 (26)
Falls risk and mobility				
FRAT score, mean ± SD	12.5±3.9	13.7±4.3	12.3±4.0	14.1±4.3
TUG, s, median (IQR)*	13.0 (10.9–16.1)	14.0 (10.5–18.7)	13.0 (10.9–16.2)	14.5 (12.0–18.7)

* Data not available for the full cohort due to missing values and/or patient-factors (in up to 2 patients per parameter).

ITT, intention to treat; COPD, chronic obstructive pulmonary disease; BMI, body mass index; TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; HDL, high density lipoprotein; CTx, collagen C-terminal telopeptide; TPO, thyroid peroxidase; QoL, quality of life; EQ-5D VAS, European five-dimensional quality of life visual analogue scale; ThyDQoL, hypothyroid-dependent quality of life; AWI-18, average weighted impact of 18 domains; FRAT, falls risk assessment tool; TUG, timed up and go test.

Markers of End-Organ Effects

As thyroid hormones have important actions on the cardiovascular system and bone, fasting lipid profile (total cholesterol, high density lipoprotein cholesterol and triglycerides), systolic and diastolic blood pressure and body weight, and the bone resorption marker serum collagen C-terminal telopeptide (CTx) were measured. Resting pulse rate and blood pressure were measured in a sitting position after 15 min rest.

Biochemical Assays

Serum TSH (reference range 0.4–4.0 mU/L), free T4 (reference range 9–5 pmol/L), free T3 (reference range 2.5–7.5 pmol/L), thyroid peroxidase antibodies (positive if >35 IU/mL) and CTx were measured by electrochemiluminescence immunoassay on the Roche Diagnostics Cobas e602. Lipid profile (Total and high density lipoprotein cholesterol and triglycerides) were measured using standard techniques (Roche Diagnostics). The within-day and between day coefficient of variation for all tests were <5% except for CTx (<20%).

Statistics

No sample size calculations were performed, as this was a feasibility study performed with the primary objective to assess participants' willingness to enter the trial, and their recruitment and retention rate. The data obtained from this trial will be utilised to inform the planning of a bigger study with longer duration of follow-up to evaluate hard outcomes. It was estimated that randomising 50 participants would provide adequate information to achieve the primary objective [26]. Analyses were carried out according to a predefined statistical analysis plan [19]. Numerical data are described as mean (SD) or median (interquartile range) depending on their distribution. Categorical data is presented as frequencies (per cent). The mean change from baseline with 95% CIs, adjusted for baseline values, is presented [27], to indicate the range of possible effects that are not excluded by the study. No hypothesis testing was performed as the study was not powered to do so. Categorical data, such as the presence of hypothyroid symptoms, is presented as percentages at both baseline and at 24 weeks. As this was a feasibility study, there was no imputation for missing data at 24 weeks and hence the analyses of change data (change from baseline to 24 weeks) are only for those participants who completed the trial. SAS/STAT software version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA) was used to perform the statistical analyses.

Results

Study invitation packs were sent to 390 potentially eligible participants identified from participating Primary Care practices (Fig. 1). Of these, 57 participants consented and were screened with biochemical thyroid function assessment and 48 participants were randomised. The baseline characteristics of these participants are described in Table 1. At screening (pre-randomisation), 10 (20.8%) participants were taking 50 μg/day, 18 (37.5%) were on 75 μg/day, 15 (31.3%) were on 100 μg/day and 5 (10.4%) were on 125 μg/day or more of LT4 therapy.

Baseline health, QoL and hypothyroid symptoms: General health and well-being (EQ-5D) visual analogue scale ("how good or bad was your health today") was reported as fair in the entire group (n = 48) with mean (± SD) score of 72.0 ± 16.6. Hypothyroid-dependent QoL, on the other hand, assessed by the ThyDQoL AWI-18, indicated an overall slightly negative perceived impact of hypothyroidism on QoL (median –0.5 [interquartile range –1.4 to 0.0]) at baseline.

Symptoms of hypothyroidism at baseline were high in the patients analysed in this study with tiredness being reported by 36/48 (75%) participants. The other symptoms that were frequently reported were problems with memory 26/48 (55%), dry skin 26/48 (55%) and feeling the cold 25/48 (52%).

Forty participants completed the study on study medication aiming for their target TSH level as randomised (21 in the ST group and 19 in the HT group). At 24 weeks, 19 out of 21 participants (90.5%) in the ST group had serum TSH within the desired target reference range (0.4–4.0 mU/L); one participant had a TSH slightly below the target range and one slightly above the target range. At the same time point in the HT group, 10 out of 19 patients (52.6%) had serum TSH within the target range (>4.0–8.0 mU/L); 3 had TSH between 0.4 and 4.0 mU/L and 6 had TSH levels above the target (>8.0 mU/L). The thyroid function and daily LT4 data at each time point is presented in Table 2. Descriptively, free triiodothyronine (FT3)/free thyroxine (FT4) ratio, used as a crude measure of deiodinase activity (in converting FT4 to the more active FT3) increased slightly, on average, in the participants in the HT arm, whereas the ratio in the ST arm remained the same (online suppl. Fig. 1, see online Supplementary Materials).

At 24 weeks, the 2 groups were clinically broadly similar on average, with regards to cardiovascular risk factors, bone resorption marker, QoL, hypothyroid symptoms or risk of falls (Tables 3, 4). In the ST arm 81% (17/21) complained of tiredness at baseline and 95% (20/21) reported tiredness at the end of the study. Similarly, in the HT group, 78% (14/18) reported tiredness at baseline and 83% (15/18) still had ongoing tiredness at the completion of the trial. Other symptoms of hypothyroidism showed no appreciable change in either arm (data not shown).

Adverse Events and Withdrawals

There were 119 adverse events (AEs) reported by 37 patients; 16 patients in the ST arm reporting 49 AEs (mean [±SD] 3.1 [±2.1] per patient) and 21 patients in the HT arm reporting 70 AEs (mean [±SD] 3.3 [±2.2]). Patients reported between 1 and 10 AEs over the course of the study. Details of AEs pertaining to the 4 most frequent complaints are described in Table 5. It is worth pointing out that AEs are any symptoms or conditions that are reported by participants to the research team and do not necessarily imply a causal association with study drug or study-related procedures.

Table 2. Thyroid function tests and levothyroxine dose by randomised treatment group and visit, completers analysis set (n = 40)

Variable, mean ± SD	Standard TSH target range (n = 21)				Higher TSH target range (n = 19)			
	n	baseline	12 weeks (visit 2)	24 weeks (visit 3)	n	baseline	12 weeks (visit 2)	24 weeks (visit 3)
TSH, mU/L	21	1.37±0.85	1.70±1.17	1.39±0.98	19	2.03±1.12	6.73±3.87	6.64±2.91
FT3, pmol/L	21	3.86±0.39	3.87±0.47	3.86±0.42	18^	3.71±0.51	3.53±0.66	3.54±0.50
FT4, pmol/L	20^^	18.74±2.68	18.85±3.07	19.42±3.53	19	18.16±2.04	15.72±2.78	15.97±2.39
FT3/FT4 ratio	20^^	0.21±0.04	0.21±0.05	0.21±0.05	18^	0.21±0.03	0.23±0.04	0.23±0.04
LT4 dose/day, μg$^{\Delta}$	21	83.3±29.9	82.1±26.4		19	83.6±25.0	57.9±25.1	

n, number of participants with non-missing data at all 3 time points. ^ FT3 missing at visit 3 for study id = 611 (so for comparative summaries over time excluded patient 611). ^^ FT4 excluded for study id = 412, genetic condition. $^{\Delta}$ Dose at visit 3 was the same as visit 2.

TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; LT4, levothyroxine.

Table 3. Mean absolute differences in cardiovascular and bone-resorption risk-markers between groups at 24 weeks, adjusted for baseline, completers analysis set (n = 40)

Outcome	Adjusted mean difference at 24 weeks, standard target TSH range minus higher target TSH range (95% CI)*
Total cholesterol, mmol/L	–0.26 (–0.57 to 0.05)
HDL cholesterol, mmol/L	–0.01 (–0.13 to 0.11)
Triglycerides, mmol/L	–0.24 (–0.61 to 0.13)
Blood pressure, mm Hg	
Systolic	0.03 (–14.3 to 14.8)
Diastolic	–0.5 (–7.0 to 6.1)
Weight, kg	–0.99 (–2.31 to 0.32)
Pulse, bpm	2.65 (–1.5 to 6.8)
CTx	0.08 (–0.04 to 0.21)

* Interpretation: at follow-up total cholesterol was on average 0.26 mmol/L lower in the standard target TSH range group compared to the higher target TSH range, taking baseline levels into account.

CTx, collagen C-terminal telopeptide; TSH, thyroid-stimulating hormone; HDL, high density lipoprotein.

Any AE that led to hospital admission, contact with a health professional or any other clinical event that was deemed serious by the local principal investigator was classed as a serious AE. There were 3 serious AEs, 2 in the ST arm and one in the HT arm.

Over the course of the 24-week follow-up period, 8 participants withdrew from the study; 3 from the ST group and 5 from the HT group. Of the participants who withdrew from the ST group, 2 reported increasing tiredness and one was confused regarding study medication and described taking the study medication concomitantly with her pre-trial LT4 tablets (although serum TSH was within the reference range at the time of trial withdrawal). Of the participants who withdrew from the HT group, 3 cited increasing tiredness, one had foot infection and one reported nausea and reduced appetite.

Discussion

The TSH reference range is derived predominantly from younger individuals, but there is increasing evidence that the serum TSH rises with age. Despite this, current clinical practice is to treat all hypothyroid patients to the same target TSH range, irrespective of age. The results of this proof of concept feasibility study suggest that aiming for a higher serum TSH in older (>80 years) hypothyroid individuals is not associated with any adverse effect over a 24-week period.

Thyroid hormones are important in regulating metabolism and have an impact on a wide array of tissues including the brain, heart, muscle and bones. Thyroid dysfunction is common, affecting all age groups with a higher frequency in women and older individuals. In the NHANES

Table 4. Quality of life, falls risk and mobility measures summary statistics; completers (n = 40)

Variable	n	Standard TSH target range (n = 21)		n	Higher TSH target range (n = 19)	
		baseline mean ± SD	mean change$^{\Omega}$ ± SD from baseline to 24 weeks		baseline mean ± SD	mean change$^{\Omega}$ ± SD from baseline to 24 weeks
Patient completed questionnaires						
EQ-5D (VAS)	21	69.0±17.4	4.9±13.4	18	74.6±16.0	−1.1±10.5
ThyDQoL (AWI-18)	19	−0.76±0.83	−0.95±1.67	18	−0.70±0.71	−0.17±1.01
Nurse-administered questionnaires						
Falls risk assessment test score	21	12.3±4.0	0.8±2.2	19	14.1±4.3	0.0±1.2
Timed up and go (time in s)	21	13.6±3.9	0.1±3.1	17	14.3±3.5	−0.2±3.8

n, number of patients with both baseline measure and week 24 measure. There could have been an observation at baseline for a patient in the completers analysis set but not at week 24, hence the n's will not always be the same here for the baseline summaries as they are in Table 1.

$^{\Omega}$ Change is calculated as visit 3 score minus visit 1 score for all variables. So, for EQ-5D (VAS) where a score of 0 equals the worst possible state and 100 equals the best possible state, a positive mean change indicates an improvement on average. For ThyDQoL (AWI-18), a negative mean change suggests a worsening of the impact of hypothyroidism on the 18 life domains measured. For the Falls risk assessment test score, a positive mean change indicates a worsening of the risk of falling. And, for the timed up and go test, a positive mean change indicates worsening of mobility whereas a negative mean change suggests an improvement.

TSH, thyroid-stimulating hormone; EQ-5D, European 5 dimensional quality of life; VAS, visual analogue scale; ThyDQoL, hypothyroid-dependent quality of life; AWI-18, average weighted impact of 18 domains.

Table 5. Common symptoms (AEs) reported by participants over the course of the trial period shown by ST and T arms*

	ST (n = 24)	HT (n = 24)
Feeling more tired, n (%)	9 (37.5)	12 (50)
Depression, n (%)	2 (8.3)	1 (4.2)
Problems with balance or mobility, n (%)	4 (16.7)	4 (16.7)
Dizziness, n (%)	2 (8.3)	2 (8.3)
Memory problems, n (%)	0	2 (8.3)

* All participants have been included to capture those that withdrew due to adverse events.

ST, standard thyrotropin; HT, higher thyrotropin; AEs, adverse events.

III survey, a study designed to provide normative estimates of health and nutritional parameters in the United States, a raised serum TSH level (>4.5 mU/L) was found in 14% of the population aged 80 years or more [4]. In the United Kingdom, the population-based Whickham study found that 10% of the population above the age of 75 years had a raised TSH level (>6.0 mU/L) [28]. There is compelling evidence that serum TSH distribution levels increase progressively with age in the reference population with the 97.5th centile being 4.03 mU/L in the 50–59-year age group and 7.49 mU/L in the 80+ age group [4]. Therefore, the prevalence of hypothyroidism is likely to be significantly overestimated and, more importantly, treatment with LT4 initiated in a proportion of these. It is recognised that over-treatment with thyroid hormones has the potential for deleterious effects on QoL, skeletal health, cardiovascular mortality and incidence of atrial fibrillation [15]. This finding has been borne out in the well-designed prospective follow-up study of 85-year-old individuals in Leiden [13]. The Leiden 85+ study showed that mortality was negatively associated with TSH levels and increased with higher FT4 levels. More importantly, in the same study, subgroup analyses after exclusion of individuals on medications for thyroid disease showed that HT and lower thyroxine levels were associated with less progression of disability, better memory and reduced mortality over 4 years of follow-up. In another study of older untreated adults aged >70 years, a mildly elevated TSH between 4.5 and 7.0 mU/L was associated with a slight functional advantage in mobility compared to those with TSH levels of 0.4–4.5 mU/L [29]. Furthermore, within the same individual, TSH levels increase over time [30, 31]. This rise in serum TSH is not associated with worse outcomes in older euthyroid individuals [14, 30, 32]. This suggests that treatment with thyroid hormones may be unnecessary and could in fact worsen outcomes in elderly individuals. In support of this, a study of older women (>65 years) found that mortality in thyroid hormone users tended to be higher with a hazard ratio (95% CI) of 1.11 (0.98–1.24) [33]. Similarly, data derived from the UK General Practitioner Research database showed that treatment of subclinical hypothyroidism with LT4 was associated with a non-significantly higher hazard ratio (>1.0) in older people, whereas a beneficial effect was observed in younger individuals [16]. A Danish registry-

based study noted that the duration of over- and under-treatment with LT4 was associated with increased cardiovascular risk although this specific finding wasn't analysed separately for individuals over 80 years [34].

The other novel finding of our study is that the FT3/FT4 ratio increased slightly on average in the HT arm, despite the reduction in exogenous thyroid hormone dose. While this phenomenon has been noted previously with LT4 monotherapy in observational cohorts [35, 36], this is the first time, as far as we are aware, that it has been shown that reducing the dose of LT4 does not have a negative impact on FT3/FT4 ratio in the same individual. This suggests that LT4 may have a direct suppressive action on deiodinase activity [37]. However, it must be stressed that the clinical implications of the FT3/FT4 ratio are unknown. Furthermore, this "apparent" slight increase on average of the FT3/FT4 ratio has been obtained from a small sample of patients and no testing was performed to assess statistical significance due to the feasibility nature of this trial. Further research is required to determine whether this ratio can be used as a marker of health, disease or thyroid hormone status.

Our study has several strengths. First, it generates proof of concept that aiming for a slightly higher target serum TSH (by reducing dose of LT4) in the over 80-year-old hypothyroid patients is feasible with no evidence of any associated adverse impact over a 24-week period. Second, the design of the study (participants were identified from 20 different General Practices over a wide geographical area, randomised, controlled and blinded to the study arm) makes the results obtained robust.

There are a number of weaknesses too. The sample size for this feasibility study was relatively small, but followed recommendations for good practice at the time the study was designed [26], and the length of follow-up was only 6 months. A full study would need to be adequately powered and have a longer duration of follow-up to be able to detect the impact of age-appropriate dosing on clinical outcomes such as cardiovascular events and mortality. Second, the number of withdrawals in this trial was relatively high (8 out of 48 participants). However, the reasons for withdrawal cited by participants in each group were broadly similar. Furthermore, other interventional studies in this age group have shown similar withdrawal rates [38]. Finally, the proportion of participants in the high TSH target arm that actually achieved the desired target was approximately half. It is likely that further dose adjustments in a trial of longer duration would be required. But, it is important to note that a high proportion of patients on LT4 therapy have abnormal TSH levels in any case [39].

In summary, this feasibility proof of concept study has shown that aiming for a higher target serum TSH in LT4-treated hypothyroid patients aged 80 years or older is not associated with any adverse outcomes. A larger adequately powered study with a longer duration of follow-up is required to assess if this has any impact on clinically relevant outcomes such as cardiovascular events, mortality, falls or fractures.

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Statement of Ethics

All participants provided written informed consent and the study was performed in concordance with the World Medical Association Declaration of Helsinki.

Disclosure Statement

Dr. Salman Razvi has received speaker fees from Merck KgA, Abbott India Pvt. Ltd., and Berlin Chemie plc, makers of LT4. All other authors have no conflicts of interest to declare.

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Author Contributions

S.R., V.R., S.H.P., and S.W.: design of study. S.R.: writing of manuscript. S.R., V.R., L.I., S.H.P., and S.W.: critical revision of the manuscript.

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