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Original Article

Treatment with levothyroxin in subclinical hypothyroidism is associated with increased mortality in the elderly☆

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ABSTRACT

Introduction: It is uncertain whether subclinical hypothyroidism should be treated with levothyroxine, particularly in the elderly. This study evaluated the association between levothyroxine treatment and mortality in individuals 65 years or older with subclinical hypothyroidism and TSH values < 10 mIU/L.

Methods: A case-control study in which patients 65 years or older with TSH levels of 4.2–10 mIU/L who died in the years 2012–2016 ('cases') were compared with matched individuals who did not die during this period ('controls'). Matching was based on gender, age, Charlson comorbidity index, date of TSH testing, duration of follow-up and TSH quartile. All cases of known thyroid disease or cases in which anti-thyroid medications or glucocorticoids were dispensed in the year preceding the TSH evaluation were excluded. Use of levothyroxine was compared between groups.

Results: During the follow-up period, 419 individuals died and these were matched with 1558 individuals who did not. Factors found to be associated with mortality were age, senile dementia, congestive heart failure, chronic renal failure and a history of cerebrovascular disease. On multivariate analysis, treatment with levothyroxine was associated with significantly increased mortality (HR = 1.19 CI 1.03–1.38). Femoral fractures and atrial fibrillation following initiation of levothyroxine therapy were not more prevalent in individuals who died during the follow-up period.

Conclusions: Treatment with levothyroxine is associated with significantly increased mortality in individuals 65 years or older with subclinical hypothyroidism and TSH < 10.

1. Introduction

The association between subclinical hypothyroidism (scH) and mortality in the elderly is debatable. Several studies have suggested that hypothyroidism in the elderly may in fact be protective [1], whereas others have suggested that there is no association between scH and mortality [2–4]. A recent study reported an association between scH and mortality with a threshold of TSH values of 6.38 mIU/L or higher [5], whereas a threshold of 10 mIU/L was suggested in other studies [6,7]. Whether levothyroxine should be routinely prescribed to individuals with scH is unclear. It is also unclear whether treatment is more beneficial in the elderly and at what TSH levels it is appropriate, if at all [8–11]. A recent prospective study [12] evaluated the functional consequences of treatment with levothyroxine in elderly patients with scH and found no beneficial effect of treatment with levothyroxine. In that study the occurrence of fatal and non-fatal cardiovascular events was only evaluated as a secondary outcome and mortality was not a predefined outcome. In this study, the association between levothyroxine treatment and all-cause mortality in elderly individuals with scH was evaluated.

2. Patients and methods

2.1. Patients

This was a case-control study in which data were collected from the Clalit Health Medical Organization (CHMO) database. As of January 2017, CHMO insures 4.4 million individuals in Israel, of which 603,000

☆ All authors had access to the data and a role in the writing of the manuscript.

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are ≥ 65 years old. The CHMO database is a comprehensive computerized data warehouse that stores demographic and medical data. Data are aggregated by continuous real-time input from physicians and health service providers, and include medical diagnosis, laboratory data and medications dispensed. The database includes all laboratory tests performed in the individual, both during hospitalization and on an outpatient basis, but for the purpose of this analysis only outpatient laboratory tests were included. Data on socioeconomic status (SES) were derived from the Israel Central Bureau of Statistics. SES was based on the SES of the clinic and categorized as low, moderate or high. For the purpose of this study we queried demographic data (age, gender, SES), co-morbidities, outpatient laboratory data, mortality data and dispensed medications. Charlson comorbidity index was used to estimate the burden of comorbidities in the study population [13]. This index contains 19 issues including diabetes mellitus, congestive heart failure, peripheral vascular disease, chronic pulmonary disease, mild and severe liver disease, hemiplegia, renal disease, leukemia, lymphoma, metastatic tumor, and acquired immunodeficiency syndrome (AIDS), each of which is weighted according to their potential influence on mortality and has been adapted and verified as applicable and valid for predicting the outcome and risk of death from many comorbid diseases.

The study population included all individuals ≥ 65 years old insured by the CHMO who had at least one serum TSH determination > 4.2 mIU/L but lower than 10 mIU/L, in 2012–2016, providing they did not have an abnormal TSH or free T4 value in the year prior to the index evaluation and that the patient did not die in the year following the initial TSH assay, to allow for sufficient levothyroxine exposure. Patients with a diagnosis of hypothyroidism or hyperthyroidism prior to the index TSH evaluation and those who were treated with systemic glucocorticoids or thionamides in the year preceding the index evaluation or with levothyroxine at any point prior to the index evaluation were excluded from the analysis. In addition, because use of medications that may affect thyroid hormone levels may significantly impact the degree of control of thyroid function [14], effect of use of medications that may affect levothyroxine absorption, (such as proton pump inhibitors, calcium and iron salts) on the association between use of levothyroxine and mortality was evaluated. This was performed based on at least two prescriptions/year of these medications. TSH values during follow-up were compared between those in which levothyroxine was initiated and those in which they were not. Follow-up data was evaluated until 30 April 2017. The study was approved by the CHMO ethics committee.

2.2. Laboratory analysis

TSH determinations were performed using the Immulite 2000 (Diagnostic Products Corp, Los Angeles, CA) and Centaur (Bayer Health Care) apparatus for which upper and lower limits are 0.35–4.2 mIU/L, as previously described [15,16]. Free T4 (fT4) determinations were performed as described [17] for which upper and lower limits are 10–20 pmol/L. These cutoffs were used based on the normal values defined by the central laboratory at CHS in which the samples were analyzed. Patients with TSH values of 4.2–10 mIU/L were included in the analysis but only if TSH values were within normal limits in the previous year and providing that free T4 values were not abnormal (< 10 pmol/L or > 20 pmol/L). All-cause mortality was compared between those treated with levothyroxine and those who were not treated during the follow up period (01/2012-04/2017). Each subject was assigned into TSH quartiles according to his first TSH value (TSH 4.2–4.47 mIU/L, 4.47–4.92 mIU/L, 4.92–5.77 mIU/L, 5.77–10 mIU/L).

3. Statistical analysis

Cases were defined as all individuals in the cohort who were living one year following the initial levothyroxine prescription, but died during the follow-up following this exposure period. For each case up to four controls were randomly selected and matched on sex, age (± 3 years), Charlson comorbidity score, calendar date of first TSH test (± 12 months), duration of follow-up and TSH quartile. Controls were assigned the same index date (mortality date) as their matched cases. Baseline characteristics of 'cases' and 'controls' were compared using Chi square tests for categorical variables, *t*-tests for continuous variables normally distributed and Mann-Whitney for continuous variables not normally distributed. A multivariable conditional logistic regression was performed to estimate odds ratios (ORs) and 95% confidence interval (CIs) for the association between levothyroxine and mortality, adjusting for age, which was not completely matched between 'cases' and 'controls', ethnicity and comorbidities. All statistical analyses were performed using SPSS 21 (SPSS Inc., Chicago, IL, USA).

4. Results

During the study period, 419 patients ≥ 65 years old with subclinical hypothyroidism and TSH levels < 10 mIU/L died and were matched with 1558 'controls'. Matching was based on gender, age, Charlson comorbidity index, date of performance of the TSH assay, duration of follow-up and TSH quartile. Baseline characteristics and comorbidities of the analyzed cohort are presented in Table 1. Senile dementia, congestive heart failure, cerebrovascular disease and chronic renal failure were all more common in the 'cases' group whereas hyperlipidemia was more common in the 'control' group.

On logistic regression analysis, use of levothyroxine in individuals with scH and TSH < 10 mIU/L was found to be associated with mortality after adjustment for sociodemographic and comorbidity confounders (Table 2). Femoral fractures and atrial fibrillation occurring after initiation of levothyroxine treatment were not more common in 'cases' group compared with the 'control' group.

Use of medications affecting levothyroxine absorption was present in almost half of patients treated with levothyroxine (43%). The association between levothyroxine treatment and mortality was more pronounced in patients treated with these medications (OR = 1.235 p = 0.085) than in those not treated with these medications (OR = 1.105 p = 0.532). Treatment with proton pump inhibitors did not affect the association with mortality, whereas treatment with iron salts was significantly associated with mortality, compared with those not treated with iron salts (OR = 4.07 vs OR = 1.165).

TSH values were evaluated in three time points following the index TSH assay. At all three time points TSH levels were significantly lower in those treated with levothyroxine compared with those not treated with levothyroxine (second assay 4.3 mIU/L vs. 5.8 mIU/L, third assay 4.4 mIU/L vs. 6.1 mIU/L fourth assay 4.4 mIU/L vs. 5.2 mIU/L p < 0.01 for all).

5. Discussion

This is the first study in the elderly in which treatment of scH was found to be associated with increased mortality. This association has been debated. A previous study reported that subclinical thyroid disease in general and scH in particular were associated with increased mortality in the elderly [5], whereas other studies reported that scH was not associated with excess mortality [18] or that TSH levels of 5–10 mIU/L may actually be protective in the elderly [19]. Another study reported that scH was associated with excess mortality only in those with congestive heart failure [20]. A recently published study reported that in patients treated with levothyroxine for scH, TSH levels in the range of 5–10 mIU/L are associated with increased mortality compared with TSH levels within the normal range and researchers therefore argued that in those who require treatment with levothyroxine, euthyroidism should be established [21]. It is questionable whether scH is a cardiovascular risk factor in itself or whether it is merely a marker of an increased cardiovascular risk independent of TSH

Table 1
Demographic characteristics of cases and controls groups.

		Cases (N = 419)	Controls (N = 1558)	All subjects (N = 1977)	p-Value
Sex	Male	99 (23.6)	362 (23.2)	461 (23.3)	0.87
	Female	320 (76.4)	1196 (76.8)	1516 (76.7)	
Age (median, IQR)		85.0 (11)	84.0 (11)	84.0 (11)	0.03
Charlson comorbidity score (median, IQR)		3.0 (3)	3.0 (3)	3.0 (3)	1
Ethnicity	Arab	8 (1.9)	21 (1.4)	29 (1.5)	0.30
	Orthodox Jewish	11 (2.6)	26 (1.7)	37 (1.9)	
	Non-orthodox Jewish	400 (95.5)	1511 (97)	1911 (96.7)	
BMI	< 18.5	7 (2.6)	8 (1.2)	15 (1.6)	0.13
	18.5–25	94 (35.5)	201 (31)	295 (32.3)	
	25–30	102 (38.5)	252 (38.8)	354 (38.7)	
	30 +	62 (23.4)	188 (29)	250 (27.4)	
TSH quartile	4.2–4.47	114 (27.2)	405 (26)	519 (26.2)	0.857
	4.47–4.92	106 (25.3)	457 (29.3)	563 (28.5)	
	4.92–5.77	115 (27.5)	434 (27.9)	549 (27.8)	
	5.77–10.0	84 (20)	262 (16.8)	346 (17.5)	
Hypertension, n (%)		362 (86.4)	1318 (84.6)	1680 (85)	0.36
Hyperlipidemia, n (%)		348 (83.1)	1358 (87.2)	1706 (86.3)	0.03
Diabetes mellitus, n (%)		175 (41.8)	684 (43.9)	859 (43.5)	0.434
Smoking, n (%)		99 (23.6)	367 (23.6)	466 (23.6)	0.98
Senile dementia, n (%)		178 (42.5)	482 (30.9)	660 (33.4)	< 0.01
Congestive heart failure, n (%)		138 (32.9)	254 (16.3)	392 (19.8)	< 0.01
Ischemic heart disease, n (%)		192 (45.8)	654 (42)	846 (42.8)	0.16
Chronic obstructive lung disease, n (%)		65 (15.5)	195 (12.5)	260 (13.2)	0.11
Chronic renal failure, n (%)		145 (34.6)	379 (24.3)	524 (26.5)	< 0.01
Cerebrovascular disease, n (%)		159 (38)	381 (24.5)	540 (27.3)	< 0.01
Atrial fibrillation, n (%)		38 (9.1)	108 (6.9)	146 (7.4)	0.14
Femoral fracture, n (%)		16 (3.8)	33 (2.1)	49 (2.5)	0.05

Table 2
Conditional logistic regression for testing the association of levothyroxine Usage and mortality, adjusting for sociodemographic and comorbidity confounders.

Variable	Adjusted OR's	p-Value	CI (95%)
Levothyroxine prescription months per year	1.19	0.000	1.03–1.38
Age	1.11	0.001	1.04–1.19
Arab ethnicity	1.63	0.27	0.69–3.85
Hypertension	1.07	0.69	0.76–1.52
Hyperlipidemia	0.74	0.08	0.53–1.03
Diabetes	1.03	0.82	0.8–1.3
Smoking	1.08	0.63	0.8–1.44
Senile dementia	1.61	0.000	1.26–2.07
Congestive heart failure	2.67	0.000	2.02–3.53
Chronic renal failure	1.89	0.000	1.42–2.51
Chronic obstructive lung disease	1.27	0.17	0.91–1.78
Cerebrovascular disease	1.94	0.000	1.5–2.52
Atrial fibrillation- after TSH test	0.936	0.76	0.61–1.43
Femur fraction- after TSH test	1.76	0.084	0.93–3.35

levels. If this is true, treatment with levothyroxine in individuals with scH may actually be detrimental as it does not treat the cardiovascular risk factors, but increases the metabolic demands of the heart and may result in ischemia associated with increased demand. The elderly is a unique population in this regard as this population has a high prevalence of cardiovascular risk factors and may be particularly vulnerable to the ill effects of tachycardia and increased cardiac output that may be caused by treatment with levothyroxine.

There is currently insufficient evidence to recommend for or against routine treatment of individuals with scH and TSH levels < 10 mIU/L. Early levothyroxine therapy does not alter the natural history of the disease, yet it may prevent symptoms and signs of overt disease in those who do progress. Still, the available data do not confirm any clear cut benefits for early therapy compared with symptom-driven therapy. Because the available data do not confirm clear-cut benefits for early levothyroxine therapy compared with treatment when symptoms of overt hypothyroidism develop [10,22], the present recommendation is to avoid routine levothyroxine replacement in individuals with TSH levels < 10 mIU/L. It is still recommended that thyroid function tests will be followed in these individuals at 6–12 months intervals to monitor for improvement or worsening in TSH levels [23]. This is the first study in which a definite association between treatment of scH and increased mortality at TSH levels < 10 mIU/L in individuals ≥ 65 years old was reported and its results are certainly a convincing argument against treatment in these individuals. Use of iron salts in patients treated with levothyroxine was found to influence the association between levothyroxine and mortality. This has two possible explanations: 1) Higher doses of levothyroxine were used in those also treated with iron salts to overcome the impaired absorption of levothyroxine induced by iron salts (the dose of levothyroxine was not available in the database although the rate of prescription was evaluated and found to be similar in those treated with iron slats and those untreated) 2) Patients treated with iron salts may have had a higher prevalence of comorbidities and thus were more prone to the effects of levothyroxine.

TSH was lower on all evaluation in patients treated with levothyroxine compared with those not treated. Yet, the difference in TSH values, although statistically significant, was minor and within the range in which there is no current recommendation to initiate treatment. Therefore we believe that the difference in mortality was not caused by this minor difference in hypothyroid control. Whether, treatment with levothyroxine in these individuals is indeed the cause for the increased mortality in these individuals is uncertain.

This study has several limitations. First, the database did not include the reason for the performance of the TSH assay or the reason for the initiation of levothyroxine treatment. This may have resulted in treatment of patients at higher risk for mortality based on comorbidities. Matching between 'cases' and 'controls' was therefore based on several factors which we believed to significantly affect survival. Second, only individuals 65 years and older were evaluated in this study and thus the results are only applicable to this age group. Another limitation of this study is that the database did not include information regarding the cause of mortality and thus the mechanism by which levothyroxine may increase mortality is unclear. In order to clarify this, we performed an analysis regarding the prevalence of atrial fibrillation and femoral fractures between 'study' and 'control' groups. These are two important

conditions that are potentially associated with treatment with levothyroxine, but both were similarly prevalent in individuals who died and those who did not during follow-up. For the purposes of this study, TSH levels of 4.21–10 mIU/L were used, because 4.21 mIU/L is defined as the upper limit of normal in the CHS laboratory in which the tests were performed. Although previous reports have recommended use of lower TSH values as the upper limit of normal [24], these values are not used for the purposes of treatment initiation in non-pregnant individuals. In addition the analysis did not include individuals with TSH values > 10 mIU/L, because at this levels most physicians would probably choose to treat the patient because of the high risk of progression to overt hypothyroidism [23].

6. Conclusions

This study provides preliminary evidence for increased mortality associated with levothyroxine treatment in individuals ≥ 65 years old with scH and TSH values < 10 mIU/L. This may serve as an important argument against initiation of L-thyroxin treatment in this population.

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None.

Conflict of interest

None.

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