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Optimal Thyroid Hormone Replacement Dose in Immune Checkpoint Inhibitor-Associated Hypothyroidism Is Distinct from Hashimoto's Thyroiditis

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Background: Immune checkpoint inhibitors (ICI) have revolutionized the treatment of many advanced cancers but are recognized to cause treatment-limiting immune-related adverse events (IrAE). ICI-associated thyroiditis is the most common endocrine IrAE and usually resolves to permanent hypothyroidism. Optimal thyroid hormone replacement in these patients remains unclear. We report the levothyroxine (LT4) dose needed to achieve stable euthyroid state in patients with hypothyroidism from ICI-associated thyroiditis, with comparison to patients with Hashimoto's thyroiditis (HT) and athyreotic state.
Methods: We conducted a retrospective study of adults with ICI-associated hypothyroidism treated with LT4 at an academic medical center. Patient data were collected from the electronic medical record. Cases had ICI exposure followed first by hyperthyroidism and then subsequent hypothyroidism. Controls were HT (positive thyroid autoantibodies, requiring LT4) and athyreotic (total thyroidectomy or radioiodine ablation, requiring LT4) patients. Patients with central hypothyroidism, thyroid cancer, pregnancy, gastrointestinal stromal tumors, and use of L-triiodothyronine were excluded. Our primary outcome compared LT4 dose needed to achieve euthyroid state (thyrotropin 0.3–4.7 mIU/L over >6 consecutive weeks) for ICI-associated hypothyroidism, HT, and athyreotic patients, considering the impact of age and possible interfering medications by linear regression modeling. Secondary analysis considered the impact of endocrine specialty care on the time to euthyroid state.
Results: One hundred three patients with ICI-associated thyroiditis were identified. Sixty-six of the 103 patients achieved euthyroid state; 2 with intrinsic thyroid gland function recovery and 64 on LT4. The mean LT4 dose achieving stable euthyroid state was $1.45 \pm$ standard deviation (SD) 0.47 mcg/[kg·day] in ICI-associated hypothyroidism, $1.25 \pm$ SD 0.49 mcg/[kg·day] in HT, and $1.54 \pm$ SD 0.38 mcg/[kg·day] in athyreotic patients, using actual body weight. The difference in dose between ICI-associated hypothyroidism and HT was statistically significant ($p = 0.0093$). Dosing differences were not explained by age or use of interfering medications.
Conclusions: ICI-associated thyroiditis represents an increasingly recognized cause of hypothyroidism. Our study demonstrates that patients with ICI-associated hypothyroidism have different thyroid hormone dosing requirements than patients with HT. Based on our findings and prior reports, we recommend that in patients with ICI-associated thyroiditis LT4 therapy be started at an initial weight-based dose of 1.45 mcg/[kg·day] once serum free thyroxine levels fall below the reference range.

Keywords: immune checkpoint inhibitor, thyroid hormone supplementation, thyroiditis

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Introduction

IMMUNE CHECKPOINT INHIBITORS (ICI) leverage the body's own immune system to eliminate tumor cells by blocking natural regulatory molecules (e.g., programmed cell death protein 1 [PD-1], programmed cell death-ligand 1 [PD-L1], and cytotoxic T lymphocyte-associated protein 4 [CTLA-4]) on immune cells that normally serve to decrease activation (1,2). ICI therapies can produce dramatic tumor shrinkage, but their use is often limited by the development of autoimmune disease affecting the skin, gut, lung, heart, endocrine organs, and nervous system. These immune-related adverse events (IrAE) occur in nearly 60% of patients (3,4). Thyroid dysfunction is the most common endocrine IrAE, occurring in ~10–15% of patients treated with ICI monotherapy and 15–25% of patients treated with combination ICI therapy (4).

ICI-associated thyroiditis has distinct features from other spontaneous forms of thyroid autoimmune disease and hypothyroidism (5–8). ICI-associated thyroiditis typically begins as an abrupt destructive phase with marked hyperthyroidism followed by a rapid conversion to hypothyroidism (8,9). Retrospective case studies suggest an increased incidence among patients with pre-existing thyroid peroxidase autoantibodies, although nearly half of patients with ICI-associated thyroid disease lack detectable serum thyroid autoantibodies (10).

More than 90% of patients with ICI-associated thyroiditis may require permanent thyroid hormone therapy for hypothyroidism (8). The American Thyroid Association promotes the use of thyroid hormone replacement dosing of 1.6 mcg/kg of body weight in patients suspected to need full thyroid hormone replacement, while expressing caution for those older than 65 years or with underlying comorbidities (11). It is nevertheless understood that thyroid hormone replacement dosing varies by the underlying cause of hypothyroidism, with athyreotic patients requiring greater thyroid hormone replacement relative to those with Hashimoto's thyroiditis (HT) to achieve euthyroid status (12).

As depicted in Table 1, prior reports of ICI-associated hypothyroidism and clinical guidelines have suggested median thyroid hormone replacement doses of 1.2 mcg/[kg·day] (range 0.25–3 mcg/[kg·day]) (8) to 1.4 mcg/[kg·day] (range 0.3–2.5 mcg/[kg·day]) (9). These reports are limited by only considering glucocorticoids as potential confounding medications and did not establish persistent euthyroid state as an endpoint. Thus, the optimal dose of thyroid hormone replacement to achieve stable euthyroid state in patients with ICI-associated hypothyroidism remains unknown.

As overtreatment with thyroid hormone medication can lead to adverse cardiovascular outcomes and increase osteoporotic fractures (13,14) and undertreatment can negatively impact quality of life (15), our study evaluates the optimal thyroid hormone dose needed to achieve stable euthyroid status in patients with ICI-associated hypothyroidism using patients with HT and athyreotic state as comparator groups.

Materials and Methods

Study design and participants

We conducted a retrospective case–controlled study of adult patients cared for within the academic medical center of the University of California Los Angeles (UCLA) Health System. Patients were identified through the UCLA Clinical and Translational Science Institute (CTSI) Bioinformatics Program using a query of the integrated clinical and research data repository. Cases and controls were defined based on International classification of diseases (ICD) codes, prescription medication inventory, and laboratory serum studies. Records were queried from January 1, 2015, to August 24, 2020.

Cases included patients exposed to an FDA-approved ICI who subsequently developed thyroid dysfunction requiring thyroid hormone replacement therapy. Controls were age- and sex-matched and consisted of two distinct groups: HT and athyreotic state. Patients were excluded if younger than 18 years on January 1, 2015; on liothyronine therapy; with pregnancy during the study period; or with a history of thyroid cancer, gastrointestinal stromal tumor [associated with expression of type 3 deiodinase (16)], or central hypothyroidism. This study involving human subjects was approved by the UCLA Institutional Review Board (IRB #20-000381).

Study definitions

Cases. ICI-associated thyroiditis was defined as ICI exposure followed by hyperthyroidism (thyrotropin [TSH] <0.3 mIU/L and, if collected within 24 hours, free thyroxine [fT4] > 1.7 ng/dL) and subsequent hypothyroidism (TSH >4.7 mIU/L) requiring thyroid hormone therapy or resolution to normal thyroid status (consecutive normal TSH levels, 0.3–4.7 mIU/L, not requiring thyroid hormone replacement).

TABLE 1. DESCRIPTION OF PRIOR STUDIES COMMENTING ON LEVOTHYROXINE DOSING IN IMMUNE CHECKPOINT INHIBITOR-ASSOCIATED HYPOTHYROIDISM

Authors	Publication year	Study type	No. of subjects	Daily LT4 dose
Chang et al. (24)	2019	Review	N/A	0.8 mcg/kg recommended as a starting dose based on clinical judgment
Iyer et al. (8)	2018	Retrospective	37	1.2 mcg/kg median dose achieving euthyroid status
Ma et al. (9)	2019	Retrospective	38	1.4 mcg/kg median dose achieving euthyroid status
Jonklaas et al. (11)	2014	National Society Guidelines	N/A	1.6–1.8 mcg/kg recommended in hypothyroid patients with minimal endogenous thyroid function

LT4, levothyroxine; N/A, not applicable.

ICI treatment regimens included: PD-1 inhibitors (pembro-lizumab, nivolumab, cemiplimab), PD-L1 inhibitors (durva-lumab, atezolizumab, avelumab), and/or a CTLA-4 inhibitor (ipilimumab). Many patients treated with ICI at our center were not treatment naive, and indeed may have been treated with prior immunotherapy. If treatment with a single ICI had a gap exceeding 12 weeks, this was considered as a separate ICI exposure, impacting evaluation of time from ICI exposure to onset of thyroiditis.

Case patients with pre-existing thyroid autoantibodies or use of levothyroxine (LT4) therapy were included if thyroid function changes met criteria of hyperthyroidism followed by hypothyroidism requiring higher doses of thyroid hormone replacement. Potential ICI-associated thyroiditis patients were excluded for lack of hyperthyroid phase; abnormal thyroid function preceding ICI therapy; concurrent acute illness more consistent with euthyroid sick syndrome; incomplete data; or history of central hypothyroidism, radioiodine ablation, external radiation-induced hypothyroidism, or thyroid surgery (Supplementary Fig. S1). The categorization of euthyroid sick syndrome was restricted to patients who had evidence of transient TSH <0.3 mIU/L in the setting of active hospitalization, acute illness not related to thyroid disease, recent surgery, on treatment for an active infection, meeting sepsis criteria, or transitioning to hospice. These patients had resolution of TSH depression without initiation of LT4 or increases in LT4 dosing.

Controls

HT control patients were defined as: a diagnosis of Hashimoto's disease, HT, or hypothyroidism-autoimmune disease (ICD-10 code E06.3, ICD-9 245.2); a prescription for LT4 during the period of January 1, 2015, to August 24, 2020; and a positive thyroid peroxidase antibody (TPOAb) and/or thyroglobulin antibody (TgAb). Patients were excluded from this control cohort for never achieving euthyroid state, use of liothyronine therapy, or history of radioiodine ablation or thyroid surgery (Supplementary Fig. S2). Because control HT patients required both evidence of autoimmunity (thyroid autoantibodies) and hypothyroidism, patients with euthyroid HT, considered to be an earlier disease state, were likely excluded.

Athyreotic control patients were identified by diagnosis codes for postprocedural hypothyroidism (ICD-10 code E89.0, ICD-9 code 244.0), which included either total thyroidectomy for benign disease or radioiodine ablation with subsequent overt biochemical hypothyroidism for benign disease; and a prescription for LT4 during the period of January 1, 2015, to August 24, 2020. Patients were excluded for never achieving euthyroid state; use of liothyronine therapy; lack of data; clarification of no history of thyroid surgery or ablation upon manual chart review; and/or a history of partial thyroidectomy, thyroid cancer, or external radiation-induced hypothyroidism (Supplementary Fig. S3).

In patients requiring LT4 among cases or controls, stable euthyroid state was defined as two consecutively normal TSH levels, 0.3–4.7 mIU/L, whose measurements were separated by at least 6 weeks.

Data collection

Patient data were collected retrospectively from the electronic medical record. Demographic data collected included age, sex, ethnicity, race, and the following relevant comorbidities: coronary artery disease (ICD-10 code 125.10; ICD-9 codes 414.01, 414.00), atrial fibrillation (ICD-10 codes I48.91, Z86.79; ICD-9 code 427.31), and osteoporosis (ICD-10 code M81.0; ICD-9 code 733.00). Cutoffs for serum TPOAb and TgAb positivity were noted according to the assay manufacturer's reference range. Malignancy categories (lung, breast, renal cell carcinoma, skin, neurological, uroepithelial, leukemia/lymphoma, and other) and endocrine specialty care were based on documented diagnoses and provider notes, respectively.

Each ICI exposure was documented with inclusion of the first exposure date and the last exposure date. Notably, if treatment with a single ICI had a gap exceeding 12 weeks, this was documented as separate ICI exposures. Potential interfering medications prescribed between January 1, 2015, and August 24, 2020, were also collected, including: estrogen, progesterone, tyrosine kinase inhibitors (TKI), calcium, iron, proton pump inhibitors (PPI), magnesium, and glucocorticoids.

Thyroid hormone medication dosing and patient weight for ICI-associated thyroiditis cases were collected during a post-hyperthyroidism period of euthyroid state, defined as two consecutively normal TSH levels whose measurements were separated by at least six weeks. For both HT and athyreotic state patients, the most recent two normal sequential TSH values separated by at least six weeks were used to define a euthyroid state to collect patient weight and LT4 hormone medication dose.

Thyroid hormone dosing for actual body weight (mcg/[kg·day]) was calculated by dividing the recorded daily dose (mcg/day) by the listed weight in kilograms. For instances where patients reported taking fewer or more than one pill per day, the average daily dose in micrograms was determined and used. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

Outcomes

The primary outcome assessed the hypothesis that the weight-based dose of LT4 required to achieve stable euthyroid state is different in patients with hypothyroidism due to ICI-associated thyroiditis compared with patients with HT or athyreotic patients. Thyroid hormone replacement dosing was compared per daily dose and body weight-based dose. Planned secondary analyses evaluated the effects of age, use of potential interfering medications (calcium, iron, TKI, magnesium, PPI, estrogen, and progesterone, and glucocorticoids), and endocrine specialty care on thyroid replacement dose and time to euthyroid state.

Statistical analyses

This study was initially designed as a matched case–control analysis. The sample size for ICI-associated thyroiditis patients was determined by availability, comprising all ICI-treated patients in the UCLA Health System meeting study eligibility criteria in the electronic medical record (commencing in 2015). Age- and sex-matched controls with HT or athyreotic state were identified in a 2:1 ratio to cases at the time of data pull from the electronic medical record using ICD diagnosis codes as described above. Upon further manual review and data abstraction of the initial cohorts,

additional patients were excluded from all groups (Supplementary Figs. S1–S3). Therefore, statistical methods accounting for matched cases and controls could not be used.

Comparisons between groups were conducted using analysis of variance (ANOVA) for continuous variables and the chi-square test (Fisher's exact test for small cell sizes) for categorical variables. The Kruskal–Wallis test was also used to compare variables that exhibited skewness. Linear regression was used to determine whether there was a statistically significant difference in the outcomes (dose/weight) between groups (ICI-associated hypothyroidism vs. HT and ICI-associated hypothyroidism vs. athyreotic patients). The models were adjusted by age (<65 and ≥65 years) as well as whether they were taking interfering medications. SAS Version 9.4 (SAS Institute, Cary, NC, USA) was used to conduct all statistical analyses. A p-value <0.05 was considered statistically significant.

Results

ICI-associated thyroiditis patients and LT4 dose requirement

A total of 103 patients were identified as meeting criteria for ICI-associated thyroiditis. Sixty-six of the 103 (64.1%) patients achieved a stable euthyroid state during the study period. Thirty-seven (35.9%) patients failed to achieve stable euthyroid state (two consecutive normal TSH evaluations separated by at least six weeks) during the study period and were excluded from subsequent comparisons with HT and athyreotic patients. Additional clinical data for these excluded cases are provided in Supplementary Table S1 and discussed later.

The baseline characteristics of the 66 ICI-associated thyroiditis cases achieving euthyroid state are listed in Table 2. ICI therapies were most commonly used for the treatment of lung (31.8%) and skin (30.3%) malignancies, and 71.2% of patients were exposed to PD-1 monotherapy, 6.1% to PD-L1 monotherapy, 3.0% to CTLA-4 monotherapy, and 19.7% to PD-1/PD-L1 + CTLA-4 combination therapy. The median time to hyperthyroidism from ICI exposure was 6.0 weeks (range 3.1–12.0 weeks): 6.0 weeks (range 3.3–12.0 weeks) for PD-1 monotherapy, 9.1 weeks (range 8.1–10.6 weeks) for PD-L1 monotherapy, 10.5 weeks (range 3.0–18.0 weeks) for CTLA-4 monotherapy, and 5.3 weeks (range 3.0–8.9 weeks) for combination therapy.

The overall median time between the onset of hyperthyroidism and euthyroid state was 23.8 weeks (range 11.7–41.4

weeks). The median time from first abnormal TSH to initiation of LT4 therapy was 12.0 weeks (25th percentile = 4 weeks, 75th percentile = 26.9 weeks). In this cohort, 2/66 (3.0%) ICI-associated thyroiditis patients achieving euthyroid state had intrinsic thyroid gland recovery and did not require thyroid hormone replacement. The mean LT4 dose achieving stable euthyroid state in persistently hypothyroid patients was 1.45 ± standard deviation (SD) 0.47 mcg/[kg·day]. This weight-adjusted dose achieving euthyroid state was significantly higher than the mean initial prescribed dose (1.16 ± SD 0.59 mcg/[kg·day], $p < 0.0001$). Regarding dose adjustments, 62.5% (40/64) required dose escalation, 25% (16/64) had no dose change, and 12.5% (8/64) required a dose reduction.

Comparison to other hypothyroid conditions

We then sought to compare the thyroid hormone replacement requirement in ICI-associated thyroiditis with other common forms of hypothyroidism: HT and athyreotic patients. A comparison of the demographic data for the 66 ICI-associated thyroiditis patients who achieved euthyroid status with HT ($N = 118$) and athyreotic ($N = 74$) controls is shown in Table 3. There were no differences across the three groups with respect to age ($p = 0.09$) or sex ($p = 0.51$), as expected from our study design. In addition, there were no differences among groups for ethnicity ($p = 0.26$), race ($p = 0.11$), BMI ($p = 0.23$), or weight ($p = 0.26$).

Thirteen of 20 (65.0%) ICI-associated thyroiditis patients had positive thyroid autoantibodies, compared with 8/21 (38.1%) athyreotic patients; all HT patients had thyroid autoantibodies as this was an inclusion criterion for this group. Comorbid coronary artery disease (27.3%), atrial fibrillation (16.7%), and osteoporosis (21.2%) were more prevalent in patients with ICI-associated thyroiditis; however, statistical significance between the three groups was only seen with coronary artery disease ($p = 0.0076$) and osteoporosis ($p = 0.0013$).

With respect to possible thyroid dose impacting medications, magnesium supplements, PPI, TKI, and glucocorticoids were used more commonly in the ICI-associated hypothyroidism patients than in the HT or athyreotic controls. No significant difference was noted in use of calcium, iron, estrogen, or progesterone (Table 4).

The mean thyroid hormone replacement dose achieving stable euthyroid state for 64 patients with persistent hypothyroidism due to ICI-associated thyroiditis is shown compared with that for HT and athyreotic controls in Table 4.

TABLE 2. TIMING OF THYROID CHANGES WITH IMMUNE CHECKPOINT INHIBITOR EXPOSURE IN IMMUNE CHECKPOINT INHIBITOR-ASSOCIATED THYROIDITIS PATIENTS WHO ACHIEVED EUTHYROID STATE

		Time from ICI exposure to onset of thyroiditis (median weeks with Q1 and Q3)	Time from ICI-thyroiditis onset to euthyroid state (median weeks with Q1 and Q3)
Treatment (ICI exposure)	$n = 66$	6.0 (3.1, 12.0)	23.8 (11.7, 41.4)
Anti-PD-1	47 (71.2%)	6.0 (3.3, 12.0)	23.6 (12.0, 36.9)
Anti-PD-L1	4 (6.1%)	9.1 (8.1, 10.6)	24.7 (13.4, 37.9)
Anti-CTLA-4	2 (3.0%)	10.5 (3.0, 18.0)	177.1 (40.0, 314.1)
Combination	13 (19.7%)	5.3 (3.0, 8.9)	16.4 (10.0, 44.0)

Combination refers to combined anti-PD-1 or anti-PD-L1 and anti-CTLA-4 immunotherapy.
CTLA-4, cytotoxic T lymphocyte-associated protein 4; ICI, immune checkpoint inhibitor; Q1, first quartile; Q3, third quartile; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1.

TABLE 3. CLINICAL PARAMETERS FOR IMMUNE CHECKPOINT INHIBITOR-ASSOCIATED THYROIDITIS, BENIGN ATHYREOTIC, AND HASHIMOTO'S THYROIDITIS PATIENTS ACHIEVING EUTHYROID STATUS

	ICI thyroiditis (n=66)	Athyreotic (n=74)	HT (n=118)	p
Age (years), mean (SD)	65.6 (12.0)	69.7 (12.9)	66.0 (12.1)	0.0854
Sex, n (%)				0.5119
Female	38 (57.6)	47 (63.5)	65 (55.1)	
Male	28 (42.4)	27 (36.5)	53 (44.9)	
Ethnicity, n (%)				0.2629
Not Hispanic or Latino	63 (95.5)	65 (87.8)	98 (83.1)	
Hispanic or Latino	1 (1.5)	7 (9.5)	13 (11.0)	
Unknown	2 (3.0)	2 (2.7)	7 (5.9)	
Race, n (%)				0.1126
White or Caucasian	53 (80.3)	47 (63.5)	89 (75.4)	
Black	1 (1.5)	6 (8.1)	9 (7.6)	
Pacific Islander	0 (0.0)	1 (1.4)	0 (0.0)	
Asian	6 (9.1)	6 (8.1)	5 (4.2)	
Other	5 (7.6)	12 (16.2)	9 (7.6)	
Unknown	1 (1.5)	2 (2.7)	6 (5.1)	
BMI (kg/m^2), mean (SD)	25.7 (4.9)	26.3 (5.4)	27.1 (5.8)	0.2339
Weight (kg), mean (SD)	73.8 (18.2)	73.0 (18.5)	77.2 (19.5)	0.2683
TPOAb or TgAb present, n (%)				<0.0001
Yes	13 (19.7)	8 (10.8)	118 (100.0)[a]	
No	7 (10.6)	13 (17.6)	0 (0.0)	
Unknown	46 (69.7)	53 (71.6)	0 (0.0)	
Comorbid diseases affected by thyroid status, n (%)				
CAD				
Present	18 (27.3)	10 (13.5)	12 (10.2)	0.0076
Absent	48 (72.7)	64 (86.5)	106 (89.8)	
Atrial fibrillation				
Present	11 (16.7)	10 (13.5)	8 (6.8)	0.0961
Absent	55 (83.3)	64 (86.5)	110 (93.2)	
Osteoporosis				
Present	14 (21.2)	12 (16.2)	5 (4.2)	0.0013
Absent	52 (78.8)	62 (83.8)	113 (95.8)	

    p Values obtained through chi-square test (or Fisher's test where appropriate) for categorical variables and ANOVA for continuous variables. Race/ethnicity was categorized such that Mexican, Mexican American, Chicano/a were grouped with Hispanic/Latino and Asian Indian, Chinese, Filipino, Japanese, Korean, Taiwanese, Vietnamese, and Other Asian with Asian.
    [a]Presence of thyroid autoantibodies was an inclusion criterion for the HT group.
    ANOVA, analysis of variance; BMI, body mass index; CAD, coronary artery disease; HT, Hashimoto's thyroiditis; TgAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody; SD, standard deviation.

A significant difference was noted in LT4 daily dose ($p=0.0050$) and LT4 weight-based dose ($p<0.0001$) among the three groups. The mean LT4 dose achieving stable euthyroid state was $1.45 \pm SD\ 0.47$ mcg/[kg·day] in ICI-associated hypothyroidism, $1.25 \pm SD\ 0.49$ mcg/[kg·day] in HT, and $1.54 \pm SD\ 0.38$ mcg/[kg·day] in athyreotic patients, using actual body weight. Generic LT4 was most frequently prescribed across the three groups, with brand name Synthroid or Tirosint less frequently used (Table 4).

To assess the differential impact of age, use of interfering medications, and etiology of hypothyroidism on thyroid hormone replacement dosing, and provide a more precise estimate of LT4 dose at euthyroid state, a linear regression analysis was performed (Table 5). Using the athyreotic group as the reference, LT4 dosing in HT controls was significantly lower ($p<0.0001$), whereas the dosing in the ICI-associated hypothyroidism group was slightly lower but did not reach statistical significance ($p=0.1589$). In this multivariate analysis, age had no significant independent effect on weight-based LT4 dose achieving euthyroid state, nor did concurrent use of magnesium, PPI, TKI, or glucocorticoid therapy.

The mean differences of dose for body weight (mcg/kg) from the adjusted linear regression showed a statistically significant difference between patients with ICI-associated hypothyroidism and HT ($p=0.0290$). No significant difference was found between thyroid hormone dose for patients with ICI-associated hypothyroidism and athyreotic controls ($p=0.1589$) (Table 5). Notably, sex was not included in the linear regression analysis as there was no difference in LT4 dose noted when each study group was stratified by sex.

Endocrine specialty care

Of the original 103 ICI-associated thyroiditis patients, 57% (29/51) who received endocrine specialty care achieved euthyroid state compared with 71% (37/52) of those who did not see an endocrinologist. The median time to euthyroid state was 21 weeks for those who had an endocrine visit compared with 27 weeks for those who did not have an endocrine visit. This difference was not statistically significant.

TABLE 4. THYROID HORMONE REQUIREMENT

	ICI thyroiditis (n = 64*)	Athyreotic (n = 74)	HT (n = 118)	p
LT4 dose				
Daily dose, mcg/day, mean (SD)	104.5 (34.75)	110.0 (30.14)	93.5 (38.42)	0.0050
Weight-adjusted dose, mcg/[kg·day], mean (SD)	1.45 (0.47)[ab]	1.54 (0.38)[ac]	1.25 (0.49)[bc]	<0.0001
Thyroid hormone formulation, n (%)				
Generic LT4	54 (84.4)	53 (71.6)	89 (75.4)	0.0912
Synthroid	9 (14.1)	21 (28.4)	29 (24.6)	
Tirosint	1 (1.6)	0 (0.0)	0 (0.0)	
Concurrent use of potentially interfering medications, n (%)				
Calcium	19 (29.7)	15 (20.3)	22 (18.6)	0.2103
Magnesium	31 (48.4)	18 (24.3)	30 (25.4)	0.0020
Iron	6 (9.4)	7 (9.5)	11 (9.3)	0.9995
PPI	49 (76.6)	37 (50.0)	48 (40.7)	<0.0001
Estrogen or progesterone	7 (10.9)	7 (9.5)	13 (11.0)	0.9367
Glucocorticoids	60 (93.8)	41 (55.4)	57 (48.3)	<0.0001
TKI	16 (25.0)	1 (1.4)	1 (0.8)	<0.0001

Thyroid hormone doses required for stable euthyroid status in patients with hypothyroidism attributed to ICI-associated thyroiditis, benign athyreotic disease, or HT, and use of potentially interfering medications and supplements. *p* Values obtained through chi-square test (or Fisher's test where appropriate) for categorical variables and ANOVA for continuous variables.
*Two ICI thyroiditis patients achieved euthyroid state without thyroid hormone replacement.
[a]*p* = 0.1900 for pairwise comparison between ICI thyroiditis versus athyreotic patients.
[b]*p* = 0.0093 for pairwise comparison between ICI thyroiditis versus HT patients.
[c]*p* ≤ 0.0001 for pairwise comparison between athyreotic patients versus HT patients.
PPI, proton pump inhibitors; TKI, tyrosine kinase inhibitors.

Patients with ICI-associated thyroiditis not achieving stable euthyroid state

While not the primary aim of this study, a comparison between those patients with ICI-associated thyroiditis who did versus did not achieve a stable euthyroid status may shed light on factors that contribute to challenges in normalization of thyroid function in this patient population. As shown in Supplementary Table S1, there was no difference in the sex, age, tumor type, or ICI therapy between patient groups. Review of these cases identified the primary reasons for failure to achieve euthyroid state as: noncompliance with medication as noted by the provider (7/37); transition to hospice (3/37), another medical center (5/37), or death (6/37) coinciding with discontinuation of thyroid care at UCLA and/or short interval of follow-up after initiation of thyroid hormone

TABLE 5. MULTIVARIATE LINEAR REGRESSION MODEL FOR PREDICTORS OF MEAN LEVOTHYROXINE DOSE ACHIEVING EUTHYROID STATUS IN HYPOTHYROID PATIENTS

Variable	Category	Regression coefficient [CI]	p
Disease group	ICI thyroiditis	−0.1245 [−0.2981 to 0.0491]	0.1589
	HT	−0.3066 [−0.4419 to −0.1712]	<0.0001
	Athyreotic	Ref	
Age >65 years	Y	−0.0877 [−0.2052 to 0.0298]	0.1430
	N	Ref	
Magnesium	Y	0.0788 [−0.0575 to 0.2151]	0.2557
	N	Ref	
PPI	Y	0.0143 [−0.1164 to 0.1450]	0.8296
	N	Ref	
Glucocorticoids	Y	0.0014 [−0.1286 to 0.1314]	0.9832
	N	Ref	
TKI	Y	−0.0423 [−0.2871 to 0.2025]	0.7337
	N	Ref	

Mean estimates of LT4 dose (mcg/kg) from adjusted linear regression

Variable	Mean difference [CI]	p
ICI thyroiditis versus HT	0.1820 [0.0188 to 0.3452]	0.0290
ICI thyroiditis versus athyreotic	−0.1245 [−0.2981 to 0.0491]	0.1589

p Values obtained through linear regression.
CI, 95% confidence interval.

(<6 weeks); subsequent development of hypophysitis with low TSH (2/37); high grade gut immunotherapy-related toxicity (1/37); or labile weight (1/37). *Post hoc* review revealed 9/37 patients in this group achieved stable euthyroid state after the end of the study period, with a mean weight-adjusted LT4 dose of 1.50 mcg/[kg·day] (SD 0.36 mcg/[kg·day]).

Discussion

ICI-associated thyroiditis represents an increasingly recognized cause of hypothyroidism in clinical practice, with evolving recommendations for diagnosis, monitoring, and treatment (17). Initiation of the optimal LT4 dose at diagnosis may minimize the adverse consequences of inadequately treated hypothyroidism or iatrogenic hyperthyroidism in these patients and improve quality of life (15). Our study reports weight-adjusted thyroid hormone replacement in a larger cohort of patients with ICI-associated hypothyroidism than previously described with the specific endpoint of stable euthyroid state over at least six weeks and with consideration of possible interfering medications beyond glucocorticoids.

Patients with persistent hypothyroidism due to ICI-associated thyroiditis required a mean LT4 dose of $1.45 \pm SD$ 0.47 mcg/[kg·day] to achieve stable euthyroid state. This is compatible with findings from two previously reported series (Table 1). Ma *et al.* identified 38 patients on PD-1 monotherapy or PD-1 and CTLA-4 combination therapy who achieved euthyroid state with a median LT4 dose of 1.4 mcg/[kg·day] (range 0.3–2.5 mcg/[kg·day]) (9). By comparison, Iyer *et al.* described a group of 37 patients with hypothyroidism following ICI therapy exposure who required a median replacement dose of 1.2 mcg/[kg·day] (range 0.25–3 mcg/[kg·day]) (8).

Interestingly, linear regression analysis of weight-based LT4 dosing found a significant association with the underlying etiology of hypothyroidism (ICI-associated thyroiditis, HT, athyreotic state) but not with age nor use of interfering medications (Table 5). Patients with ICI-associated hypothyroidism required a significantly higher weight-adjusted LT4 dose to achieve stable euthyroid state compared with those with HT. Although the mean difference in the required dose was quantitatively small, the finding suggests a difference in initial dosing between patients as many standard doses vary by as little as 12–25 mcg. By comparison, adjusted LT4 dosing was found to be similar between those with ICI-associated hypothyroidism and athyreotic state.

This may reflect the fulminant inflammation and gland destruction seen in patients with ICI-associated thyroiditis (8) compared with more gradual forms of hypothyroidism. Thus, our results may not necessarily be generalizable to patients who develop progressive hypothyroidism during ICI treatment without a preceding thyroiditis phase. Patients with mild hypothyroidism in the setting of TKI therapy (18) and cases of coincident spontaneous autoimmune thyroiditis (e.g., HT) while on ICI therapies may also require different LT4 doses. Central hypothyroidism related to ICI-induced hypophysitis was not evaluated in this study.

Overall, the time to onset of hyperthyroidism in our ICI-treated patients was similar to prior studies (8,19,20), with a median time of 6.0 weeks, as was the prevalence of thyroid autoantibodies, present in 65.0% of our ICI-associated thyroiditis patients (10). For the 66 case patients achieving euthyroid state, the median time between the onset of hyperthyroidism and euthyroid state was 23.8 weeks (range 11.7–41.4 weeks). As serum TSH is expected to reflect thyroid hormone dosing changes after ∼6 weeks, the time to euthyroid state of nearly 6 months serves as a reminder of the difficulty in managing ICI-associated hypothyroidism and the value of etiology-specific thyroid hormone dosing recommendations.

Another reason for this long duration to euthyroid state could be prior lack of standardization of the monitoring frequency of thyroid function tests while a patient is on thyroid hormone replacement. As of February 2021, the National Comprehensive Cancer Network has set forth guidelines that in hypothyroidism, thyroid function tests should be monitored every 4–6 weeks to guide thyroid hormone dosing when adjustments are made (21). More consistent thyroid hormone testing with the help of oncologists and primary care physicians may have captured an earlier achievement of euthyroid status.

Half of the patients (51/103) with ICI-associated thyroiditis were treated by an endocrinology specialist and 57% (29/51) achieved euthyroid state. By comparison, 37 of 52 (71%) patients without endocrine care achieved euthyroid state ($p = 0.1536$). It is possible that patients who are deemed more complicated or challenging to manage may preferentially have been referred to endocrinology.

Based on our findings and prior reports, we recommend that in patients with ICI-associated thyroiditis, LT4 therapy be started at an initial weight-based dose of 1.45 mcg/[kg·day] once serum fT4 levels fall below the reference range. Given the often rapidly changing thyroid function status in these patients, once identified, it is our routine practice to measure TSH and fT4 with every immunotherapy cycle, approximately every four weeks. Because of the potential lag of TSH after hyperthyroidism, we monitor both TSH and fT4 levels during this dynamic phase.

Furthermore, our data show that in routine clinical practice many patients were started on a lower LT4 dose (mean 1.16 mcg/[kg·day]) and required dose escalation to achieve the euthyroid state. Given that many patients are not managed by an endocrinologist, at least initially, a more precise dose recommendation for ICI-associated thyroiditis may optimize the care of these patients and lead to more rapid achievement of euthyroid status. When the pattern of ICI-associated thyroiditis is clear, providers should consider initiation of the initial weight-based LT4 replacement dose of 1.45 mcg/[kg·day] at diagnosis.

Our study is inherently limited by its retrospective nature and modest sample size. Specifically, the intervals in laboratory evaluation and medication adjustment were driven by the standard of care. For example, TSH values are routinely checked with every cycle of ICI at our institution (typically every 3–4 weeks), but much less frequently in patient with HT or athyreotic state. In addition, some patients with ICI-associated thyroiditis may have been excluded if the hyperthyroid phase was not captured by the standard laboratory interval. Dose adjustments for thyroid hormone replacement were also at the discretion of the treating provider and not done in a protocolized manner. Patient compliance with medication was not controlled or assessed prospectively.

Multiple known factors influencing thyroid hormone dose requirements were considered in our study design. However, some factors unique to ICI-treated patients, such concurrent gut immunotherapy toxicity, were not well captured by

medical coding and documentation and therefore could not be included in our analysis. Atrial fibrillation and osteoporosis were relatively common in our ICI-associated thyroiditis patients and are known to be exacerbated by prolonged and severe TSH suppression (<0.03 mIU/L) (22). The incidence of significant iatrogenic hyperthyroidism should be evaluated in future studies. Finally, our study was specifically focused on ICI-associated thyroiditis, defined as a period of ICI-induced initial hyperthyroidism that transitions to hypothyroidism (8,17,23). Future prospective studies are warranted to evaluate the proposed weight-based dose of LT4 in patients with ICI-associated thyroiditis as well as other forms of hypothyroidism seen in cancer patients on ICI therapy.

Conclusions

Using a retrospective case–controlled design, we demonstrated that patients with ICI-associated hypothyroidism have thyroid hormone dosing requirements that differ from those with HT but are not significantly different than those with athyreotic state. These data can help guide thyroid hormone replacement dosing at diagnosis to minimize the adverse consequences of inadequately treated hypothyroidism or iatrogenic hyperthyroidism.

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Authors' Contributions

T.M., K.T., S.S., H.W., N.K.-P., S.S.P., A.D., T.E.A., and M.G.L. conceived the study and designed the analysis. T.M., K.T., S.S., N.K.-P., and M.G.L. contributed to data extraction and analysis. H.W. performed and oversaw the primary statistical analyses. T.M., K.T., S.S., H.W., and N.K.-P. prepared the tables and figures. T.M., K.T., S.S., H.W., N.K.-P., S.S.P., A.D., T.E.A., and M.G.L. wrote or edited the article. All authors reviewed the article and agreed to be included as co-authors.

Author Disclosure Statement

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Supplementary Material

Supplementary Figure S1
Supplementary Figure S2
Supplementary Figure S3
Supplementary Table S1

References

1. Wei SC, Duffy CR, Allison JP 2018 Fundamental mechanisms of Immune Checkpoint Blockade Therapy. Cancer Discov **8:**1069–1086.
2. Postow MA, Sidlow R, Hellmann MD 2018 Immune-related adverse events associated with Immune Checkpoint Blockade. N Engl J Med **378:**158–168.
3. Arnaud-Coffin P, Maillet D, Gan HK, Stelmes JJ, You B, Dalle S, Péron J 2019 A systematic review of adverse events in randomized trials assessing immune checkpoint inhibitors. Int J Cancer **145:**639–648.
4. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao CD, Cowey CL, Schadendorf D, Wagstaff J, Dummer R, Ferrucci PF, Smylie M, Hogg D, Hill A, Márquez-Rodas I, Haanen J, Guidoboni M, Maio M, Schöffski P, Carlino MS, Lebbé C, McArthur G, Ascierto PA, Daniels GA, Long GV, Bastholt L, Rizzo JI, Balogh A, Moshyk A, Hodi FS, Wolchok JD 2019 Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med **381:**1535–1546.
5. Angell TE, Min L, Wieczorek TJ, Hodi FS 2018 Unique cytologic features of thyroiditis caused by immune checkpoint inhibitor therapy for malignant melanoma. Genes Dis **5:**46–48.
6. Delivanis DA, Gustafson MP, Bornschlegl S, Merten MM, Kottschade L, Withers S, Dietz AB, Ryder M 2017 Pembrolizumab-induced thyroiditis: comprehensive clinical review and insights into underlying involved mechanisms. J Clin Endocrinol Metab **102:**2770–2780.
7. Kurimoto C, Inaba H, Ariyasu H, Iwakura H, Ueda Y, Uraki S, Takeshima K, Furukawa Y, Morita S, Yamamoto Y, Yamashita S, Katsuda M, Hayata A, Akamatsu H, Jinnin M, Hara I, Yamaue H, Akamizu T 2020 Predictive and sensitive biomarkers for thyroid dysfunctions during treatment with immune-checkpoint inhibitors. Cancer Sci **111:**1468–1477.
8. Iyer PC, Cabanillas ME, Waguespack SG, Hu MI, Thosani S, Lavis VR, Busaidy NL, Subudhi SK, Diab A, Dadu R 2018 Immune-related thyroiditis with immune checkpoint inhibitors. Thyroid **28:**1243–1251.
9. Ma C, Hodi FS, Giobbie-Hurder A, Wang X, Zhou J, Zhang A, Zhou Y, Mao F, Angell TE, Andrews CP, Hu J, Barroso-Sousa R, Kaiser UB, Tolaney SM, Min L 2019 The impact of high-dose glucocorticoids on the outcome of immune-checkpoint inhibitor-related thyroid disorders. Cancer Immunol Res **7:**1214–1220.
10. de Moel EC, Rozeman EA, Kapiteijn EH, Verdegaal EME, Grummels A, Bakker JA, Huizinga TWJ, Haanen JB, Toes REM, van der Woude D 2019 Autoantibody development under treatment with immune-checkpoint inhibitors. Cancer Immunol Res **7:**6–11.
11. Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, Celi FS, Cooper DS, Kim BW, Peeters RP, Rosenthal MS, Sawka AM 2014 Guidelines for the Treatment of Hypothyroidism: prepared by the American Thyroid Association Task Force on Thyroid Hormone Replacement. Thyroid **24:**1670–1751.
12. Gordon MB, Gordon MS 1999 Variations in adequate levothyroxine replacement therapy in patients with different causes of hypothyroidism. Endocr Pract **5:**233–238.
13. Lechner MG, Hershman JM (2018/2022) Thyroid nodules and cancer in the elderly. In: Feingold KR, Anawalt B, Boyce A, *et al.* (eds). Endotext [Internet, www.endotext.org, accessed January 11, 2022]. MDText.com Inc., South Dartmouth, MA; 2000-2022.

14. Delitala AP, Scuteri A, Doria C 2020 Thyroid hormone diseases and osteoporosis. J Clin Med **9:**1034.
15. Gulseren S, Gulseren L, Hekimsoy Z, Cetinay P, Ozen C, Tokatlioglu B 2006 Depression, anxiety, health-related quality of life, and disability in patients with overt and subclinical thyroid dysfunction. Arch Med Res **37:**133–139.
16. Maynard MA, Marino-Enriquez A, Fletcher JA, Dorfman DM, Raut CP, Yassa L, Guo C, Wang Y, Dorfman C, Feldman HA, Frates MC, Song H, Jugo RH, Taguchi T, Hershman JM, Larsen PR, Huang SA 2014 Thyroid hormone inactivation in gastrointestinal stromal tumors. N Engl J Med **370:**1327–1334.
17. Quandt Z, Young A, Perdigoto AL, Herold KC, Anderson MS 2021 Autoimmune endocrinopathies: an emerging complication of immune checkpoint inhibitors. Annu Rev Med **72:**313–330.
18. Lechner MG, Vyas CM, Hamnvik OR, Alexander EK, Larsen PR, Choueiri TK, Angell TE 2018 Risk factors for new hypothyroidism during tyrosine kinase inhibitor therapy in advanced nonthyroidal cancer patients. Thyroid **28:**437–444.
19. Yamauchi I, Sakane Y, Fukuda Y, Fujii T, Taura D, Hirata M, Hirota K, Ueda Y, Kanai Y, Yamashita Y, Kondo E, Sone M, Yasoda A, Inagaki N 2017 Clinical features of nivolumab-induced thyroiditis: a case series study. Thyroid **27:**894–901.
20. Kotwal A, Kottschade L, Ryder M 2020 PD-L1 inhibitor-induced thyroiditis is associated with better overall survival in cancer patients. Thyroid **30:**177–184.
21. Reid PD, Cifu AS, Bass AR 2021 Management of immunotherapy-related toxicities in patients treated with immune checkpoint inhibitor therapy. JAMA **325:**482–483.
22. Flynn RW, Bonellie SR, Jung RT, MacDonald TM, Morris AD, Leese GP 2010 Serum thyroid-stimulating hormone concentration and morbidity from cardiovascular disease and fractures in patients on long-term thyroxine therapy. J Clin Endocrinol Metab **95:**186–193.
23. Osorio JC, Ni A, Chaft JE, Pollina R, Kasler MK, Stephens D, Rodriguez C, Cambridge L, Rizvi H, Wolchok JD, Merghoub T, Rudin CM, Fish S, Hellmann MD 2017 Antibody-mediated thyroid dysfunction during T-cell checkpoint blockade in patients with non-small-cell lung cancer. Ann Oncol **28:**583–589.
24. Chang LS, Barroso-Sousa R, Tolaney SM, Hodi FS, Kaiser UB, Min L 2019 Endocrine toxicity of cancer immunotherapy targeting immune checkpoints. Endocr Rev **40:**17–65.

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