

Levothyroxine dose requirements in a thyroid cancer- predominant cohort: a target-aware analysis of gastrointestinal and medication-related factors

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Abstract

Purpose

In thyroid cancer, optimal TSH level is particularly important, but high levothyroxine (LT4) doses may reflect intentional thyroid-stimulating hormone (TSH) suppression rather than impaired bioavailability. We assessed gastrointestinal and medication-related factors in relation to LT4 dose after accounting for treatment goals and body mass index (BMI).

Methods

This cross-sectional study included 218 LT4-treated patients and 69 non-LT4 reference patients. A structured questionnaire captured gastrointestinal symptoms, comorbidities, medications, and administration timing. BMI was calculated from recorded height and weight. The primary analysis included target-achieved patients with complete covariate data and used multivariable regression with HC3 robust standard errors.

Results

Among LT4-treated patients, 201 (92.2%) had thyroid cancer, 81 (37.2%) reported gastrointestinal symptoms, 74 (33.9%) had at least one potential interfering factor, and 49 (22.5%) reported proton-pump inhibitor (PPI) use. Factor prevalence was comparable in the reference population after adjustment for age, sex, and BMI. In the BMI-adjusted model ($n = 156$), PPI use was not associated with higher LT4 dose ($\beta = -0.031$ $\mu\text{g/kg/day}$, 95% CI -0.193 to 0.131 ; $P = 0.703$). Intended TSH suppression was associated with higher dose ($\beta = 0.420$, 95% CI 0.269 – 0.570 ; $P < 0.001$), whereas BMI was inversely associated with dose per kilogram. An absolute-dose model adjusted for weight and height confirmed the null PPI result.

Conclusion

Potentially interfering factors were common but did not independently explain increased dose requirements. LT4 dose in thyroid cancer should be interpreted in relation to therapeutic intent and anthropometry; PPI exposure alone was not a reliable marker of increased dose requirement.

Introduction

Levothyroxine (LT4) is one of the most frequently prescribed medicines and remains the standard treatment for hypothyroidism and thyroid hormone replacement after thyroidectomy [1, 2]. Because LT4 has a narrow therapeutic range, relatively small changes in bioavailability, administration conditions, or treatment goals may lead to clinically relevant changes in thyroid-stimulating hormone (TSH). Tablet dissolution begins in the stomach, whereas absorption occurs predominantly in the small intestine;

consequently, gastric pH, gastrointestinal disease, food, and concomitant medication may influence treatment performance [2].

Potentially interfering conditions and exposures are common in routine care. In the CONTROL Surveillance Project, almost half of surveyed LT4-treated patients reported a gastrointestinal condition with potential relevance to treatment. At the same time, supplements and prescription or over-the-counter medication were also frequent [3]. Large observational studies have reported changes in TSH or LT4 prescribing after initiation of iron, calcium, proton-pump inhibitors (PPIs), estrogens, and other potentially interacting drugs [4, 5]. Increased LT4 requirements have also been described in patients with *Helicobacter pylori*-associated or atrophic gastritis, celiac disease, and lactose intolerance [6–8].

PPIs are of particular interest because an increase in gastric pH may impair dissolution of tablet LT4 [2]. A systematic review of seven interventional and observational studies found that TSH increased after concomitant PPI exposure in all included studies. However, study designs and effect estimates were heterogeneous and did not support a pooled quantitative estimate [9]. Subsequent clinical findings have remained inconsistent. A prospective crossover study demonstrated an increase in TSH during pantoprazole treatment irrespective of morning or evening administration [10]. In contrast, a randomized study of patients receiving stable LT4 doses found no clinically relevant change during omeprazole treatment [11]. These differences indicate that the effect of a single exposure cannot be interpreted independently of the underlying disease, treatment duration, administration behavior, LT4 formulation, and therapeutic target.

This issue is especially relevant in thyroid cancer care. LT4 may be prescribed either for physiological replacement or for pharmacological TSH suppression, and contemporary management emphasizes dynamic, individualized treatment goals according to disease status and treatment response [12]. A retrospective cohort of 215 patients with thyroid cancer identified sex, preoperative free thyroxine, T stage, and body mass index as predictors of achieving the expected TSH level [13]. A 2025 systematic review and meta-analysis of 11 studies comprising 2,577 patients found that only 33.9% were euthyroid at the first assessment after total thyroidectomy and that no initial dosing strategy was consistently superior [14]. In a multicenter cohort of 1,016 patients with low-risk differentiated thyroid cancer, treatment adequacy under the 2015 ATA targets was 26.0% at 12 months and 39.5% at the final follow-up [15]. Applying the broader, response-adapted 2025 ATA criteria reclassified treatment adequacy to 40.7% and 67.4%, respectively [16], illustrating how strongly the definition of an appropriate dose depends on the therapeutic framework.

The central clinical problem is therefore interpretive. In primary hypothyroidism, an unexpectedly high LT4 dose commonly raises concern about non-adherence or impaired absorption. In thyroid cancer, however, the same dose may be entirely appropriate because TSH suppression is the intended treatment. If the therapeutic target is not incorporated, associations between PPI use, gastrointestinal conditions, and LT4 dose may be confounded by treatment intent. They may lead to patients being incorrectly classified as having impaired absorption or inadequate treatment.

Existing studies have largely addressed either potential treatment interference in primary hypothyroidism or achievement of risk-adapted TSH targets after thyroid cancer treatment, but rarely both within the same analytical framework. Anthropometry adds a further interpretive layer: dose expressed per kilogram of actual body weight generally decreases as BMI increases, and BMI has been associated with TSH target achievement after thyroid cancer treatment [13, 14]. To our knowledge, few studies have jointly evaluated gastrointestinal symptoms, potentially interfering conditions, concomitant medication, therapeutic intent, and BMI in a thyroid cancer-predominant cohort. We therefore assessed the prevalence and documentation of these factors, compared their frequency with a non-LT4 reference population, and examined their independent association with LT4 dose among patients who had achieved their intended TSH target.

Materials and methods

Study design and participants

This was a cross-sectional analysis of prospectively collected routine-care questionnaire data from the specialized thyroid outpatient clinic of the Department of Nuclear Medicine, University Hospital Marburg. Questionnaires were distributed consecutively to patients undergoing a thyroid examination between 1 October 2023 and 31 March 2024. The inferential dose analyses comprised 218 respondents receiving LT4. Sixty-nine respondents not receiving LT4 were retained as a descriptive reference population for the frequency of gastrointestinal symptoms and potential interfering factors; they were not used as controls for LT4 dose requirement because they had no LT4 exposure or dose outcome.

The anonymized evaluation was approved by the Ethics Committee of the Medical Faculty, Philipps University Marburg (23–194 ANZ) and was conducted in accordance with the Declaration of Helsinki. The requirement for individual informed consent for the retrospective analysis of anonymized routine-care data was waived by the responsible ethics committee.

Questionnaire and clinical variables

The structured questionnaire recorded age, sex, body weight, thyroid disease, LT4 dose and treatment duration, comorbidities, concomitant medication, and the interval between LT4 and other medication. Gastrointestinal symptoms comprised nausea, vomiting, heartburn, diarrhea, and flatulence and were reported in frequency categories. The questionnaire additionally captured PPI use, medication for gastrointestinal symptoms, medical treatment for gastrointestinal disease, inflammatory bowel disease, gastritis, *Helicobacter pylori* infection, gastric or duodenal ulcer, previous gastric or intestinal surgery, celiac disease, lactose intolerance, gastroparesis, liver cirrhosis, and pancreatic dysfunction. Body height was added from the clinical record where available. The original German questionnaire and an English translation are provided as Online Resource 1.

Serum TSH and a clinician-recorded assessment of the intended treatment goal were extracted from the clinical dataset. The latter indicated whether TSH suppression was intended and whether the patient was considered to have achieved the individualized target at the time of assessment. Numerical patient-specific TSH target ranges, American Thyroid Association risk categories, and response-to-therapy categories were not available in structured form.

Data preparation and definitions

The patient-level dataset was reconstructed from the original workbook, retaining one record per participant. Original questionnaire codes were preserved, and analysis variables were derived before statistical testing. BMI was calculated as body weight in kilograms divided by squared body height in meters. Weight-adjusted LT4 dose was recalculated as prescribed daily dose divided by body weight and expressed as $\mu\text{g}/\text{kg}/\text{day}$. No height or BMI values were imputed.

For descriptive purposes, TSH was classified reproducibly as suppressed (< 0.1 mU/L), slightly suppressed ($0.1\text{--}0.3$ mU/L), within the laboratory euthyroid range ($> 0.3\text{--}4.0$ mU/L), or elevated (> 4.0 mU/L). These laboratory categories were not used as a substitute for the individualized treatment goal.

The primary PPI exposure was PPI use documented in the structured concomitant-medication section. Because PPI use was also queried in the risk-factor section, a sensitivity exposure was defined as a positive response in either section. The structured supplement variable combined calcium, iron, vitamin D, vitamin B12, magnesium, and related supplements; individual agents could not be reliably separated.

A gastrointestinal symptom was considered present when the corresponding frequency code was greater than zero. A gastrointestinal disease composite included medical treatment for a gastrointestinal disorder, inflammatory bowel disease, gastritis, *Helicobacter pylori* infection, gastric or duodenal ulcer, celiac disease, lactose intolerance, gastroparesis, liver cirrhosis, or pancreatic dysfunction. PPI use and previous gastrointestinal surgery were modeled separately.

Outcomes and statistical analysis

The primary outcome was weight-adjusted LT4 dose in $\mu\text{g}/\text{kg}/\text{day}$, interpreted as an indirect measure of dose requirement rather than a direct measure of intestinal absorption. The primary population comprised patients documented as having achieved their intended TSH target and with complete data for BMI and the prespecified covariates. This restriction was chosen because a dose observed above or below the intended target may not represent a stabilized dose requirement.

Continuous variables are presented as median and interquartile range (IQR), and categorical variables as number and percentage. Wilson 95% confidence intervals (CIs) were calculated for selected prevalence estimates. Unadjusted continuous and categorical comparisons used the Mann-Whitney U test and Fisher exact test, respectively. Within the target-achieved population, median dose differences and 95%

CIs were estimated using 20,000 nonparametric bootstrap samples. Associations between ordinal counts and dose were evaluated using Spearman correlation, and comparisons across more than two groups used the Kruskal-Wallis test. Exploratory comparisons between the LT4-treated and non-LT4 populations were additionally evaluated by logistic regression adjusted for age, sex, and BMI among adults with complete anthropometric data.

The primary adjusted analysis used multivariable ordinary least-squares regression with HC3 robust standard errors. The dependent variable was LT4 dose in $\mu\text{g/kg/day}$. Prespecified covariates were PPI use, age per 10 years, sex, LT4 treatment duration per 5 years, intended TSH suppression, the combined supplement variable, gastrointestinal disease, gastrointestinal surgery, and observed BMI per 5 kg/m^2 . Thyroid disease indication was not included because 155 of 156 complete cases had thyroid cancer, precluding stable estimation of an indication effect. The inverse BMI coefficient was interpreted cautiously because body weight contributes to both BMI and the denominator of the outcome.

Model diagnostics included the Breusch-Pagan test, Jarque-Bera test, variance inflation factors, leverage, and Cook distance. Sensitivity analyses omitted BMI to retain all otherwise complete cases, used the combined PPI definition, restricted the population to thyroid cancer, included all patients with known target status while adjusting for target achievement, excluded observations with Cook distance greater than $4/N$, used median regression, and repeated the analysis in the numerically euthyroid subgroup. An anthropometric sensitivity model used absolute LT4 dose in $\mu\text{g/day}$ and adjusted for recorded weight and height. Missing data were handled by complete-case analysis without imputation. Tests were two-sided; $P < 0.05$ was considered significant for the primary PPI coefficient. Secondary analyses were exploratory and not adjusted for multiple testing. Analyses were performed using Sigma Plot 15.0, Python 3.13.5, NumPy 2.3.5, SciPy 1.17.0, and statsmodels 0.14.6.

Results

Cohort and reference-population characteristics

The LT4-treated cohort comprised 218 patients, of whom 148 (67.9%) were female, and 201 (92.2%) were treated for thyroid cancer. Median age was 53 years (IQR 41–65), median height was 169 cm (IQR 163–177; $n = 195$), median weight was 78 kg (IQR 66–93; $n = 213$), and median BMI was 27.3 kg/m^2 (IQR 24.1–31.7; $n = 195$). Median LT4 treatment duration was 6 years (IQR 2–12; $n = 214$). The median daily LT4 dose was 150 μg (IQR 112–175), corresponding to 1.78 $\mu\text{g/kg/day}$ (IQR 1.49–2.08; $n = 213$) (Table 1).

Table 1

Clinical and anthropometric characteristics of the LT4-treated cohort and non-LT4 reference population

Characteristic	LT4-treated cohort	Non-LT4 reference	P value
Participants	218	69	-
Age, years	53 [41–65]	58 [48–71]	0.036
Female sex	148 (67.9%)	42 (60.9%)	0.308
Height, cm	169 [163–177]	169 [163–174]	0.604
Weight, kg	78.0 [66.0–93.0]	71.5 [63.0–81.8]	0.001
BMI, kg/m ²	27.3 [24.1–31.7]	25.2 [22.1–27.7]	0.001
Any GI symptom	81 (37.2%)	23 (33.3%)	0.667
Any potential interfering factor	74 (33.9%)	22 (31.9%)	0.884
PPI use, medication section	49 (22.5%)	8 (11.6%)	0.057
PPI use, either section	58 (26.6%)	19 (27.5%)	0.877
Thyroid cancer indication	201 (92.2%)	-	-
LT4 treatment duration, years	6 [2–12]	-	-
LT4 dose, µg/day	150 [112–175]	-	-
LT4 dose, µg/kg/day	1.78 [1.49–2.08]	-	-
TSH, mU/L	0.19 [0.02–1.00]	-	-
Individual target achieved	175/205 (85.4%)	-	-
Continuous variables are presented as median [interquartile range] and categorical variables as n (%). P values are unadjusted and descriptive. Available anthropometric data: LT4 height/BMI n = 195 and weight n = 213; reference height/BMI n = 57 and weight n = 62. The reference population was not used for LT4 dose analyses. LT4, levothyroxine; BMI, body mass index; GI, gastrointestinal; PPI, proton-pump inhibitor.			

Median TSH was 0.19 mU/L (IQR 0.02–1.00). Ninety-two patients (42.2%) had a suppressed TSH, 28 (12.8%) had a slightly suppressed TSH, 88 (40.4%) were within the laboratory euthyroid range, and 10 (4.6%) had an elevated TSH. Target status was available for 205 patients; 175 (85.4% of those with known status) were documented as having achieved the intended target. The clinical characteristics of the ten patients with elevated TSH are summarized in Online Resource 2.

The non-LT4 reference population comprised 69 patients, of whom 42 (60.9%) were female. Median age was 58 years (IQR 48–71), height 169 cm (IQR 163–174; n = 57), weight 71.5 kg (IQR 63.0–81.8; n = 62), and BMI 25.2 kg/m² (IQR 22.1–27.7; n = 57). The LT4 cohort had a higher unadjusted BMI (P = 0.001),

whereas height and sex distribution were similar (Table 1). BMI was available for 89.4% of the LT4 cohort and 82.6% of the reference population.

Prevalence of potential interfering factors and routine-care documentation

At least one gastrointestinal symptom was reported by 81 LT4-treated patients (37.2%; 95% CI 31.0-43.7%) and 23 reference patients (33.3%). Considering all non-zero frequency categories in the LT4 cohort, flatulence was reported by 63 patients (28.9%), heartburn by 53 (24.3%), diarrhea by 50 (22.9%), nausea by 45 (20.6%), and vomiting by 36 (16.5%) (Table 2). Among 250 adults with complete BMI data, LT4-treatment status was not associated with gastrointestinal symptoms after adjustment for age, sex, and BMI (adjusted odds ratio 1.14, 95% CI 0.59–2.20; P = 0.691).

Table 2
Gastrointestinal symptoms and potential factors interfering with levothyroxine therapy

Factor	n (%)	95% CI, %
Any gastrointestinal symptom	81 (37.2%)	31.0-43.7
Flatulence, any frequency	63 (28.9%)	-
Heartburn, any frequency	53 (24.3%)	-
Diarrhea, any frequency	50 (22.9%)	-
Nausea, any frequency	45 (20.6%)	-
Vomiting, any frequency	36 (16.5%)	-
Any potential interfering factor (source score)	74 (33.9%)	28.0-40.5
PPI, medication section	49 (22.5%)	17.4–28.5
PPI, risk-factor section	54 (24.8%)	-
PPI, either section	58 (26.6%)	-
Combined supplement variable	26 (11.9%)	-
Gastrointestinal disease composite	30 (13.8%)	-
Previous gastrointestinal surgery	18 (8.3%)	-
Medication timing documented	75 (34.4%)	-
The combined supplement variable included calcium, iron, vitamin D, vitamin B12, magnesium, and related supplements. PPI, proton-pump inhibitor; CI, confidence interval.		

At least one questionnaire-defined potential interfering factor was present in 74 LT4-treated patients (33.9%; 95% CI 28.0-40.5%) and 22 reference patients (31.9%). PPI use was recorded in 49 LT4-treated

patients (22.5%) in the medication section and in 54 (24.8%) in the dedicated risk-factor section; 58 (26.6%) were positive in either section. Corresponding figures in the reference population were 8 (11.6%), 17 (24.6%), and 19 (27.5%), respectively. After adjustment for age, sex, and BMI, LT4-treatment status was not associated with any potential factor (adjusted odds ratio 1.15, 95% CI 0.58–2.30; $P = 0.686$) or PPI use under the combined definition (adjusted odds ratio 0.93, 95% CI 0.43–2.01; $P = 0.850$). The medication-section PPI difference remained non-significant (adjusted odds ratio 2.45, 95% CI 0.93–6.48; $P = 0.070$).

In the LT4 cohort, the combined supplement variable was positive in 26 patients (11.9%), the gastrointestinal disease composite in 30 (13.8%), and previous gastrointestinal surgery in 18 (8.3%) (Table 2). The interval between LT4 and other medication was documented for 75 of 218 patients (34.4%), corresponding to 75 of 137 patients (54.7%) reporting concomitant medication. The median interval was 30 minutes (IQR 17.5–82.5; range 0–900 minutes); because timing data were incomplete and likely not missing at random, this variable was not entered into adjusted models.

Dose requirement after achievement of the individualized TSH target

Among the 175 patients documented as having achieved their intended TSH target, 40 reported PPI use, and 135 did not. Weight-adjusted dose was available for 39 PPI users and 133 non-users. Median LT4 dose was 1.63 $\mu\text{g/kg/day}$ (IQR 1.36–2.05) in PPI users and 1.81 $\mu\text{g/kg/day}$ (IQR 1.58–2.14) in non-users. The median difference was $-0.18 \mu\text{g/kg/day}$ (bootstrap 95% CI -0.34 to 0.12 ; $P = 0.082$), providing no unadjusted evidence of a higher dose among PPI users.

PPI users were older than non-users (median 62.5 vs 52.0 years; $P = 0.001$), whereas BMI was similar (27.9 vs 27.1 kg/m^2 ; $P = 0.174$). Gastrointestinal disease was more common in PPI users (30.0% vs 8.1%; $P < 0.001$), illustrating potential confounding by indication. In the numerically euthyroid subgroup, median LT4 dose was 1.40 $\mu\text{g/kg/day}$ among PPI users and 1.56 $\mu\text{g/kg/day}$ among non-users ($P = 0.934$).

In the target-achieved population, median LT4 dose was 1.80 $\mu\text{g/kg/day}$ in patients with no questionnaire risk factor, 1.81 $\mu\text{g/kg/day}$ in those with one factor, and 1.67 $\mu\text{g/kg/day}$ in those with more than one factor ($P = 0.314$). The number of gastrointestinal symptoms was not correlated with LT4 dose (Spearman $\rho = 0.061$, $P = 0.427$). Other unadjusted comparisons are shown in Table 3.

Table 3

Unadjusted comparisons of weight-adjusted levothyroxine dose in patients who achieved their intended TSH target

Exposure	Exposed / unexposed N	Median dose exposed / unexposed	Median difference (95% CI)	P value
PPI use	39 / 133	1.63 [1.36–2.05] / 1.81 [1.58–2.14]	-0.18 (-0.34 to 0.12)	0.082
Any gastrointestinal symptom	63 / 109	1.82 [1.60–2.14] / 1.79 [1.49–2.08]	0.04 (-0.13 to 0.20)	0.516
Gastrointestinal disease composite	22 / 150	1.67 [1.34–1.94] / 1.81 [1.54–2.14]	-0.14 (-0.43 to 0.10)	0.106
Previous gastrointestinal surgery	15 / 157	1.70 [1.61–2.04] / 1.80 [1.52–2.13]	-0.10 (-0.24 to 0.26)	0.929
Dose is expressed as µg/kg/day and presented as median [interquartile range]. Median-difference confidence intervals were estimated using 20,000 bootstrap samples — CI, confidence interval; GI, gastrointestinal; PPI, proton-pump inhibitor.				

Target-aware multivariable and sensitivity analyses

The primary BMI-adjusted complete-case model included 156 target-achieved patients. PPI use was not associated with a higher LT4 dose ($\beta = -0.031$ µg/kg/day, 95% CI -0.193 to 0.131; $P = 0.703$). Intended TSH suppression was associated with a higher dose ($\beta = 0.420$, 95% CI 0.269–0.570; $P < 0.001$), as was longer treatment duration ($\beta = 0.055$ µg/kg/day per 5 years, 95% CI 0.010–0.100; $P = 0.017$). BMI was inversely associated with dose expressed per kilogram ($\beta = -0.178$ µg/kg/day per 5 kg/m², 95% CI -0.245 to -0.110; $P < 0.001$). Age, sex, combined supplement use, gastrointestinal disease, and gastrointestinal surgery were not independently associated with dose (Table 4).

Table 4
Primary BMI-adjusted multivariable regression of weight-adjusted levothyroxine dose

Predictor	Adjusted β , $\mu\text{g/kg/day}$	95% CI	P value
PPI use	-0.031	-0.193 to 0.131	0.703
Age, per 10 years	-0.048	-0.096 to 0.001	0.055
Female sex	-0.079	-0.214 to 0.055	0.246
LT4 duration, per 5 years	0.055	0.010 to 0.100	0.017
TSH suppression intended	0.420	0.269 to 0.570	< 0.001
Combined supplement variable	0.040	-0.136 to 0.217	0.651
Gastrointestinal disease composite	0.008	-0.231 to 0.246	0.949
Previous gastrointestinal surgery	-0.179	-0.552 to 0.195	0.346
BMI, per 5 kg/m^2	-0.178	-0.245 to -0.110	< 0.001
N = 156 complete cases. Ordinary least-squares regression with HC3 robust standard errors. Model $R^2 = 0.394$; adjusted $R^2 = 0.357$. Coefficients are expressed as $\mu\text{g/kg/day}$. BMI, body mass index; CI, confidence interval; GI, gastrointestinal; LT4, levothyroxine; PPI, proton-pump inhibitor; TSH, thyroid-stimulating hormone.			

The model explained 39.4% of variability in weight-adjusted dose (adjusted $R^2 = 0.357$). There was no evidence of heteroscedasticity (Breusch-Pagan $P = 0.262$) or material multicollinearity (maximum variance inflation factor 1.24). Residuals deviated from normality (Jarque-Bera $P = 0.001$); therefore, inference relied on HC3 robust standard errors and was supported by median-regression and influence-restricted sensitivity analyses.

The null PPI finding was consistent across sensitivity analyses (Table 5). The complete-case model without BMI retained 170 patients and yielded $\beta = -0.080 \mu\text{g/kg/day}$ (95% CI -0.244 to 0.084; $P = 0.336$). Using PPI positivity in either questionnaire section, restricting the cohort to thyroid cancer, adjusting the full known-target cohort for target achievement, excluding seven influential observations, applying median regression, and restricting the analysis to numerically euthyroid patients all produced estimates whose confidence intervals crossed zero. In the absolute-dose model adjusted for recorded weight and height, PPI use was likewise not associated with dose ($\beta = -6.39 \mu\text{g/day}$, 95% CI -20.81 to 8.03; $P = 0.383$).

Table 5
Sensitivity analyses for the association between PPI use and levothyroxine dose

Analysis	N	PPI coefficient	95% CI	P value
Primary BMI-adjusted model	156	-0.031	-0.193 to 0.131	0.703
Complete-case model without BMI	170	-0.080	-0.244 to 0.084	0.336
PPI positive in either section + BMI	156	0.056	-0.104 to 0.217	0.488
Thyroid-cancer-only + BMI	155	-0.043	-0.203 to 0.117	0.594
Full known-target cohort + BMI	184	0.021	-0.125 to 0.167	0.778
Excluding Cook distance > 4/N	149	0.013	-0.117 to 0.144	0.841
Median regression + BMI	156	0.046	-0.135 to 0.227	0.616
Numerically euthyroid subgroup + BMI	68	0.002	-0.249 to 0.253	0.986
Absolute dose + recorded weight and height	156	-6.39 µg/day	-20.81 to 8.03	0.383
Coefficients are expressed as µg/kg/day except for the absolute-dose model, which is expressed as µg/day. BMI, body mass index; CI, confidence interval; PPI, proton-pump inhibitor.				

Across all models, PPI coefficients were small and did not show a consistent positive direction. Intended TSH suppression remained the strongest positive correlate of dose. The inverse BMI association in the weight-normalized model, together with the stable null PPI result in the absolute-dose model, demonstrates that both therapeutic intent and anthropometric scaling are required for clinically meaningful interpretation of LT4 dose.

Discussion

This study addresses a clinically important interpretive gap in LT4 management: a high dose may suggest impaired bioavailability in primary hypothyroidism. Still, it may be deliberately prescribed to achieve TSH suppression after thyroid cancer. Four findings are clinically relevant. First, potential interfering symptoms, diseases, and medications were common but occurred at comparable frequencies in a non-LT4 thyroid-clinic population. Second, PPI use did not predict a higher LT4 dose after restricting the analysis to patients at their intended target and adjusting for BMI and clinical covariates. Third, intended TSH suppression was the strongest positive correlate of dose. Fourth, BMI materially influenced dose expressed per kilogram, emphasizing that therapeutic intent and anthropometry must be considered together.

The target-aware and anthropometrically adjusted design is the key methodological strength of the present analysis. The cohort comprised 218 LT4-treated patients, more than 90% of whom had thyroid cancer, and BMI was available for 89.4%. Unlike most interaction studies, which examined TSH changes in primary hypothyroidism, the primary analysis evaluated dose requirement in patients documented as

having reached their individualized goal. The non-LT4 reference population provided context showing that broad gastrointestinal symptoms and risk factors were not specific to LT4 treatment. Reproducible data cleaning, robust multivariable regression, and multiple sensitivity analyses, including an absolute-dose model based on recorded weight and height, support the consistency of the null PPI finding.

The prevalence findings identify actionable gaps in routine care. In the CONTROL Surveillance Project, 47% of LT4-treated patients reported at least one potentially relevant gastrointestinal condition [3]. In our cohort, the burden was lower but remained substantial and was similar to the non-LT4 reference population after adjustment for age, sex, and BMI. Thus, the mere presence of gastrointestinal symptoms or a broad risk factor is not a specific marker of increased LT4 requirement. PPI status was discordant between questionnaire sections in 13 LT4-treated patients, and the interval between LT4 and other medication was documented in only 54.7% of those reporting concomitant medication. A focused medication reconciliation recording agent, dose, duration, indication, and interval from LT4 is likely to be more clinically useful than an unstructured medication list.

The absence of an independent PPI-dose association should not be interpreted as evidence that gastric pH is irrelevant to tablet LT4. Experimental dissolution data support a pH-dependent mechanism [17], and the 2021 systematic review found increased TSH after combined tablet LT4 and PPI use across all seven included studies [9]. However, those studies were heterogeneous in population, PPI regimen, follow-up, and outcome definition. A prospective crossover study found a rise in TSH after six weeks of pantoprazole [10], whereas a randomized study found no clinically relevant change during three months of omeprazole [11]. Our study adds a different and clinically necessary perspective: it asks whether PPI exposure independently explains the stabilized dose required to reach an individualized target in thyroid cancer follow-up. In this setting, it did not.

The clinical implication is a sequence of interpretation. In a patient with thyroid cancer, the individualized TSH target and whether it has been achieved should be established before a high LT4 dose is attributed to impaired absorption. In a stable patient at target, PPI exposure alone should not be treated as proof of increased dose requirement or as an automatic indication for dose escalation or formulation change. Conversely, persistent failure to reach the intended target despite verified administration remains a reason for focused evaluation of adherence, food and medication timing, specific interacting agents, and gastrointestinal disease. This target-first approach may reduce unnecessary dose changes while directing diagnostic effort toward patients with genuine biochemical instability.

The association between intended TSH suppression and LT4 dose is clinically coherent and demonstrates why a target-aware framework is necessary. The 2025 ATA guideline recommends repeated reassessment of TSH goals according to recurrence risk, disease status, treatment response, and potential adverse effects [12]. Anthropometry provides a second essential dimension. BMI has been associated with TSH target achievement in thyroid cancer [13], and post-thyroidectomy studies show limitations of simple actual-body-weight dosing [14]. In our primary model, higher BMI was associated with a lower dose per kilogram, an expected pattern partly amplified by the presence of body weight in

both BMI and the outcome denominator. Importantly, an absolute-dose model adjusted for recorded weight and height preserved the null PPI result. The study therefore extends previous literature by integrating treatment goal, gastrointestinal exposures, and observed anthropometry in the same analysis.

The lack of significant associations for gastrointestinal disease, gastrointestinal surgery, or the number of symptoms and risk factors also requires cautious interpretation. These exposures were relatively uncommon, and broad questionnaire categories cannot distinguish active, severe disease from mild or treated conditions. Patients with recognized problems may already have modified their administration behavior or received empirical dose adjustments. Accordingly, the present findings do not exclude clinically relevant effects in selected individuals; they show that the mere presence of broad risk categories did not independently identify patients with higher dose requirements once the individualized treatment goal was considered.

Alternative LT4 formulations were not investigated and should not dominate interpretation of this study. Selected patients with persistent biochemical instability despite verified adherence and administration may benefit from a formulation less dependent on gastric dissolution. Studies have reported improved TSH control after switching from tablets to liquid LT4 in patients receiving PPIs, with lactose intolerance, after bariatric surgery, or with gastric disease [18–21]. The present data suggest that such decisions should follow, rather than precede, confirmation of the individual treatment target and a structured review of adherence, timing, and specific exposures.

Several methodological considerations define the scope of the present analysis and point to useful directions for future research. The study was designed to evaluate clinically observable LT4 dose requirements rather than to quantify intestinal absorption directly. Prospective studies incorporating LT4 absorption testing, serial free-thyroxine kinetics, and longitudinal dose adjustment could therefore extend the present findings by adding a mechanistic dimension. The questionnaire-based assessment reflects routine clinical practice; linking future data collection to prescription records and structured documentation of medication dose, duration, indication, and timing would permit more detailed evaluation of PPI, calcium, and iron exposure. Anthropometric data were available for most participants, while complete height measurements together with numerical TSH targets, ATA recurrence-risk categories, and response-to-therapy classifications could further refine target-aware modeling. The non-LT4 population was intentionally used to provide clinical context rather than causal comparison. Finally, the specialized single-center, thyroid cancer-predominant cohort offers a well-defined setting in which to develop this target- and BMI-aware framework; multicenter prospective studies could assess its applicability across broader thyroid populations and evaluate whether structured medication review improves biochemical stability and treatment efficiency.

Conclusion

Gastrointestinal symptoms, comorbidities, and concomitant medications with the potential to interfere with LT4 therapy were common but were not specific to LT4 treatment and did not independently explain increased dose requirements. Intended TSH suppression was the strongest positive correlate of dose, while BMI affected the interpretation of dose normalized to actual body weight. A high LT4 dose should therefore not be equated with malabsorption without first accounting for the individualized treatment goal and anthropometry. This target- and body-size-aware approach can improve medication review, avoid unnecessary dose changes, and focus further evaluation on patients with genuine biochemical instability.

Declarations

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Consent to participate: The requirement for individual informed consent was waived for the retrospective analysis of anonymized routine-care data.

Consent for publication: Not applicable.

Data availability: The de-identified data supporting the findings of this study are available from the corresponding author on reasonable request, subject to institutional and data-protection requirements.

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