Levothyroxine Replacement in Obese Adults: The Role of Metabolic Variables and Aging on Thyroid Testing Abnormalities

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Context: General rates of over- and underreplacement in levothyroxine (LT4) users with primary hypothyroidism are variably high. No information on LT4 adequacy exists in obesity.

Objective: We explored rates and factors relating to LT4 adequacy in obese patients with primary hypothyroidism.

Setting: Tertiary care center.

Design: Among 4954 consecutive obese patients admitted between 2011 and 2014, 691 hypothyroid patients receiving LT4 therapy and 691 body mass index (BMI)-, age-, and sex-matched euthyroid controls underwent analysis of thyroid function, glucolipid profile, body composition, and indirect calorimetry. LT4 users were classified into low TSH (<0.27 mU/L), euthyroid (0.27 to 4.2 mU/L), and high TSH (>4.2 mU/L).

Results: LT4 users constituted 13.9% of the incident population. TSH was low in 7.5%, high in 17.2%, and normal in 75.2% of LT4 users. Overtreatment decreased with aging and more LT4 users ≥65 years of age had normal TSH than those <65 years of age ($P < 0.05$). Compared with the euthyroid obese group, LT4 users showed higher adiposity, similar insulin resistance, but a healthier lipid profile. In multivariable analyses, LT4 dose was predicted by fat-free mass, hypothyroidism cause, and sex ($P < 0.0001$ to < 0.05). Risk of LT4 overreplacement increased with younger age (OR 0.96; 95% CI 0.94 to 0.99), higher LT4 dose (OR 2.98; 95% CI 1.44 to 6.14), and lower BMI (OR 0.93; 95% CI 0.88 to 0.99). Male sex increased the likelihood of LT4 underreplacement (OR 2.37; 95% CI 1.10 to 5.11).

Conclusions: Obesity is associated with milder rates of inadequate LT4 treatment compared with nonobese populations. LT4 adequacy increases with aging. Age, body composition, and sex are main determinants of LT4 requirements in obesity. **(*J Clin Endocrinol Metab* 104: 6265–6274, 2019)**

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Received 1 April 2019. Accepted 26 June 2019.
First Published Online 2 July 2019

Abbreviations: AITD, autoimmune thyroid disease; BMI, body mass index; CHO, cholesterol; CRP, C-reactive protein; %FM, percent fat mass; FFM, fat-free mass; FT3, 3,5,3′-triiodothyronine; FT4, free thyroxine; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; LDL, low-density lipoprotein; LT4, levothyroxine; REE, resting energy expenditure; T2DM, type 2 diabetes mellitus; TG, tryglycerides; WC, waist circumference.

Obesity and thyroid abnormalities are common conditions closely linked together from clinical and molecular viewpoints (1). This relation has become clinically relevant in the context of an unprecedented increase in the prevalence of obesity worldwide (2). Because thyroid hormone plays important roles in energy homeostasis and glucolipid metabolism (1), thyroid dysfunctions are often associated with perceived or factual changes in body composition and resting energy expenditure (REE) independent of physical activity (3).

Levothyroxine (LT4) is the treatment of choice when the diagnosis of persistent thyroid hormone deficiency is confirmed (4–6). With the exception of central hypothyroidism or peripheral thyroid hormone resistance, individualized LT4 dose up-titration is conventionally determined by circulating TSH, the established biomarker of LT4 replacement (7–11). Reaching a TSH value within the age-adjusted euthyroid range is the accepted therapeutic target (4, 5, 12–14) because it promotes improvements in symptoms, quality of life, and cardiovascular risk (15–22). The therapeutic management of primary hypothyroidism with LT4 is considered relatively uncomplicated and aided by reliably accurate TSH and thyroid hormone immunoassays. Despite reaching TSH within the euthyroid range, however, some patients face modest improvements in body weight and lipid abnormalities during long-term LT4 replacement (5, 23, 24). Moreover, epidemiology studies found that as many as 57% of patients undergoing LT4 replacement can experience therapy over- or underreplacement, even when frequent biochemical monitoring is accomplished (13, 25–27). Aspects of previously unrecognized complexity in the therapeutic management of hypothyroidism have also been underscored in special populations, specifically older patients, children, pregnant women, and obese individuals (4–6, 13, 14, 28). Common reasons for incorrect LT4 replacement include nonadherence, medication administration errors, dietary factors, medication interference, as well as impaired LT4 absorption (4–6, 14, 29–31).

To date, the rate of abnormal thyroid function testing and its metabolic associates in obese subjects undergoing LT4 treatment of primary hypothyroidism remains unknown. Given the detrimental consequences of inadequate LT4 replacement especially in the aging population, we conducted a cross-sectional investigation to define the prevalence and the factors associated with inadequate LT4 replacement and to evaluate the metabolic phenotype associated with LT4-treated hypothyroidism in obese patients.

Patients and Methods

Of 4954 consecutive *de novo* patients admitted between 7 January 2011 and 28 December 2014 to our institution for workup and rehabilitation of morbid obesity, 691 obese patients suffering from primary hypothyroidism on stable treatment with tablet LT4 for at least six months were included in the (605 females/86 males; age, 59 years [interquartile range (IQR), 50 to 69 years]; body mass index [BMI], 43.9 kg/m^2 [IQR 40.1 to 48.4 kg/m^2]). All patients' charts were individually reviewed where available to exclude inappropriate LT4 prescriptions. The cause of primary hypothyroidism was autoimmune thyroid disease (AITD) in 609 patients (88.1%) and total thyroidectomy in 82 cases (11.9%). None had had thyroid cancer. A group of 691 BMI-, age-, and sex-matched biochemically euthyroid obese patients referred to our unit for obesity in the same period were enrolled according to the exclusion criteria and comprised the control group. Exclusion criteria were comorbidities affecting the evaluation of thyroid function, acute illness and/or acute inflammation, use of T3 or medications potentially interfering with thyroid function (such as amiodarone, steroids, or lithium carbonate therapy) or LT4 absorption (such as cholestyramine, antacids, ferrous sulfate, sucralfate, laxatives, calcium carbonate, proton pump inhibitors, lovastatin, bile acid sequestrants), and pregnancy. In all patients, body weight was stable for six months or longer prior to study enrolment. The investigation was approved by the local ethics committee, functioning according to the fourth edition of the *Guidelines on the Practice of Ethics Committees in Medical Research With Human Participants* (32) on admission, and written consent was obtained from all patients. Main study outcomes included rates of over- and undertreatment in LT4 users and factors associated with LT4 adequacy. Secondary outcome measures included assessment of differences in metabolic profile between LT4 users and euthyroid controls.

In all participants, body measurements were conducted on fasting patients wearing light underwear. Weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, and BMI was expressed as body mass (kg)/height (m^2). The criterion of obesity was BMI $\geq$ 30 kg/m^2. Waist circumference (WC) was measured midway between the lowest rib and the top of the iliac crest after gentle aged expiration; hip was measured as the greatest circumference around the nates. Bioimpedance analysis (BIA, 101/S Akern; Florence, Italy) allowed measurement of percent fat mass (%FM) expressed and fat-free mass (FFM, kg). Methodology, variation coefficients, and exclusion criteria have been detailed previously (33). Resting energy expenditure (REE) was expressed in kilocalories per 24 hours and determined in a thermoregulated room (22°C to 24°C) by computed open-circuit indirect calorimetry, measuring resting oxygen uptake and resting carbon dioxide production by a ventilated canopy (Sensormedics, Milan, Italy) at 1-minute intervals for 30 minutes and expressed as 24-hour value. Methodology, equation formulae, and performance of different equations to predict measured REE have been described previously (33, 34).

Undiluted serum samples were assayed in duplicate for fT4 and TSH using an automated chemiluminescence assay system (Immulite 2000; DPC, Los Angeles, CA). The principle of the method is a two-site, solid-phase chemiluminescent immunometric assay or competitive immunoassay. LT4 users were classified according to TSH levels, into one of the following three groups: patients with low serum TSH levels (TSH $<$ 0.27 mU/L), euthyroid patients (TSH 0.27 to 4.20 mU/L), and patients with high serum TSH (TSH $>$ 4.20 mU/L). Within these groups, patients were then stratified according to their free thyroxine (fT4) levels: high (fT4 $>$17.0 ng/L), normal (fT4 $\geq$ 9.0 to 17.0 ng/L), and low fT4 (fT4 $<$ 9 ng/L).

Obese euthyroid controls underwent measurement of antithyroperoxidase and antithyroglobulin antibodies by automated chemiluminescence assay system (Anti-Tg, Anti-TPO Ready Pack, Siemens Healthcare Diagnostics, Milan, Italy). Thyroid ultrasound examination was performed in a subgroup of 47 controls having their TSH levels above the reference TSH range to exclude antibody-negative AITD. Routine laboratory data included glucose, total cholesterol (CHO), high-density (HDL) and low-density lipoprotein (LDL) cholesterol and triglycerides (TG) measured by enzymatic methods (Roche Diagnostics, Mannheim, Germany). Ultrasensitive C-reactive protein (CRP) was measured by CRP (latex) HS Roche kit. Insulin levels were measured using a Cobas Integra 800 Autoanalyzer (Roche Diagnostics, Indianapolis, IN, USA), and insulin resistance was expressed as homeostatic model assessment of insulin resistance (HOMA-IR) [insulin (mIU/L) × glucose (mmol/L)/22.5]. Type 2 diabetes mellitus (T2DM) was ascertained by patients' history and/or biochemistry analyses on admission according to current guidelines (35).

Statistical analyses

Statistical analyses were performed using SPSS version 21 (IBM Corp., Armonk,, NY) on log transformed data to correct for the non-Gaussian distribution obtained by the Shapiro-Wilk test. In the text and tables, values are expressed as median and IQRs. Univariate ANOVA was used for comparison between groups. Spearman correlation analysis was used to identify associations between the variables of interest.

Stepwise multivariable regression analysis was conducted to identify predictors of LT4 dose and the multilinear model included age, sex (female = 0, male = 1), BMI, FFM and %FM, REE, etiology of hypothyroidism (AITD = 0, total thyroidectomy = 1), daily LT4 dose in micrograms per kilogram of body weight (BW), duration of LT4 treatment, and T2DM. β coefficients and significance values obtained from the models were reported. Multinomial logistic regression analysis was performed to test the effect of variables of interest on the risk of under- and overtreatment with LT4 therapy. Statistical significance was set at 5%.

Results

Obese LT4 users

LT4 users accounted for 3.9% of all patients referred to our unit in the study period for morbid obesity. Most patients of the study population were severely obese: BMI was >40 kg/m^2 in 75.8%, >35.0 to 39.9 kg/m^2 in 18.4%, and >30.0 to 34.9 kg/m^2 in 5.8% of LT4 users; females accounted for 87.6%. Previously diagnosed or *de novo* T2DM affected 47.7% of cases. Anthropometric and metabolic profiles are summarized in Table 1.

In the population as a whole, the median daily dose of LT4 was 100 μg (IQR, 75 to 125), equivalent to 0.91 μg/kg/d (IQR, 0.61 to 1.17) when expressed relative to BW. As expected, the daily LT4 micrograms per kilogram dose was lower in AITD than athyreotic patients [0.85 (IQR, 0.55 to 1.10) vs 1.20 μg/kg/d (IQR, 0.91 to 1.40), $P < 0.01$]. The difference in LT4 micrograms per kilogram dose between females and males was not substantial [0.84 (IQR, 0.45 to 1.16) vs 0.91 μg/kg/d (IQR, 0.61 to 1.17), respectively].

The overall rate of patients with abnormal TSH was 24.7%. Individually, TSH levels were low in 7.5% (52 cases: TSH < 0.27 to 0.1 mU/L in 27 and < 0.1 mU/L in 25), high in 17.2% (119 cases; TSH > 4.20 to 10 mU/L in 101 and > 10 mU/L in 18) and normal in the remaining

Table 1. Summary of Anthropometric and Biochemical Data Obtained in Obese LT4 Users and Obese Euthyroid Controls

Variables	LT4 Group (n = 691)	Eu-Thyr Group (n = 691)	*P*
Males/females, N, %	86/605 (12.4/87.6)	86/605 (12.4/87.6)	1
Age, y	59 (50–69)	58.0 (50.9–66)	0.9
BMI, kg/m^2	43.9 (40.1–48.4)	44.3 (39.8–48.2)	0.5
BMI > 40 kg/m^2	75.8%	77.6%	0.2
Waist, cm	123 (114–132)	122 (111–131)	0.6
FM, %	50.9 (46.6–54.2)	48.9 (44.4–53.0)	<0.0001
FFM, kg	54.0 (48.3–59.8)	54.4 (49.1–61.6)	0.2
REE, kcal/d	1731 (1557–1940)	1711 (1491–1949)	0.2
REE_{FFM}	31.5 (2.6–34.4)	30.7 (27.1–33.8)	<0.001
TSH, mU/L	2.08 (0.96–3.69)	1.78 (1.20–2.70)	<0.0001
FT4, ng/L	12.1 (10.8–13.6)	11.2 (10.2–12.5)	<0.0001
Glucose, mg/dL	97.0 (88.0–114.8)	97.0 (86.0–111.0)	0.1
Insulin, mU/L	13.1 (8.9–18.4)	13.4 (9.6–18.9)	0.2
HOMA–IR	3.2 (2.1–4.8)	3.3 (2.2–5.2)	0.1
CHO, mg/dL	191 (166–219)	208 (182–233)	<0.0001
LDL-CHO, mg/dL	120 (97–144)	129 (106–153.9)	<0.0001
HDL-CHO, mg/dL	47 (39–56)	47 (39–54)	0.7
TG, mg/dL	130 (100–175)	130 (103–169)	0.5
CRP, mg/dL	0.7 (0.4–1.2)	0.7 (0.4–1.2)	0.7

Data are expressed as median, with IQR in parentheses, or as percentage. Comparison between populations was performed by ANOVA and χ^2 test.

Abbreviation: Eu-Thyr Group, obese euthyroid controls.

75.3% of cases. Moreover, high FT4 levels were observed in 13.4% of patients with low TSH, whereas 12.6% of those with high TSH had low FT4 levels. According to serum TSH, the rate of undertreated patients was higher than that of overtreated ones (χ^2 = 17.80, $P < 0.0001$). Compared with LT4 users whose TSH was in the euthyroid range (Table 2), overreplaced patients were younger, less obese, and took a higher daily dose of LT4 in micrograms per kilogram, whereas underreplaced patients were younger, predominantly male, showed higher abdominal obesity, FFM, insulin and insulin resistance, and took a lower daily dose of LT4 in micrograms per kilogram. A declining trend in FFM-adjusted REE was observed with decreasing LT4 replacement. In analysis restricted to LT4 users with diabetes on long-term metformin treatment, this subgroup exhibited nonsignificantly lower TSH levels compared with LT4 users without diabetes [TSH, 1.83 (IQR, 0.34 to 3.46) vs 2.6 (IQR, 0.01 to 3.25) mU/L; $P = 0.7$], whereas proportions of overtreated (5.2% vs 7.3%) and undertreated (15.7% vs 13.0%) patients were comparable between subgroups.

TSH levels did not appear to change with increasing age (Fig. 1). In the 238 LT4 users aged ≥65 years, however, the frequency of euthyroid TSH was marginally higher than in the younger counterpart (84% vs 70.6%, $P < 0.05$), because of a progressive reduction in overtreatment rates across increasing age decades (Fig. 2). Cumulatively, low TSH levels suggestive of overtreatment were observed in <5% of patients aged >65 years, whereas the rate of those with high TSH remained relatively constant across age decades. Sex distribution was similar between elderly and nonelderly subgroups. The anthropometric and metabolic study showed that elderly LT4 users had a lower body weight, were more sarcopenic, and, expectedly, took a lower LT4 dose than their younger counterpart (Table 3).

Table 2. Summary of Data Obtained in Obese LT4 Users, Subdivided as Adequately, Undertreated, and Overtreated Patients

Variables	Adequately Treated (n = 519)	Undertreated (n = 119)	Overtreated (n = 52)
Males/females, N, %	50/469 (9.6/90.4)	30/89 (25.2/74.8)[a]	6/46 (11.5./98.5)[aa]
Age, y	60 (51–70)	57 (49–64)[b]	54 (48–63)[c]
BMI, kg/m^2	44.1 (40.2–48.5)	44.5 (41.0–49.6)	40.6 (37.1–43.7)[c,bb]
Waist, cm	123 (113–132)	127 (116–139)[b]	120 (110–125)[b,cc]
FM, %	51.0 (47.2–54.5)	49.5 (43.6–53.9)	50.0 (44.7–53.0)
FFM, kg	53.7 (47.9–58.8)	58.6 (50.9–68.4)[a]	51.1 (47.7–56.8)[dd]
REE, kcal/d	1720 (1549–1920)	1809 (1631–2057)[b]	1711 (1570–1904)
REE_{FFM}	31.5 (28.6–34.4)	30.5 (27.7–33.3)[b]	32 (30.2–35.5)[aa]
LT4 dose, μg/d	100 (75–125)	100 (50–136)	125 (92–150)[d,aa]
LT4 dose BW, μg/kg/d	0.90 (0.62–1.14)	0.84 (0.49–1.14)[b]	1.16 (0.94–1.37)[c,bb]
TSH, mU/L	1.80 (1.02–2.80)	5.90 (4.92–8.12)[a]	0.07 (0.03–0.15)[a,bb]
FT4, ng/L	12.1 (11.0–13.6)	11.1 (9.9–12.4)[a]	14.3 (12.7–16.0)[a,bb]
Glucose, mg/dL	96 (88–113)	101 (90–119)	95 (88–107)
Insulin, mU/L	12.7 (8.9–17.7)	14.3 (8.8–21.8)[b]	13.8 (9.6–18.3)
HOMA-IR	3.0 (2.1–4.6)	3.6 (2.1–6.0)[b]	3.2 (2.2–5.0)
CHO, mg/dL	192 (168–218)	189 (166–226)	181 (155–213)
LDL-CHO, mg/dL	120 (99–143)	121 (95–147)	104 (89–140)
HDL-CHO, mg/dL	47 (38–57)	46 (40–55)	47 (41–53)
TG, mg/dL	127 (102–174)	141 (100–183)	126 (85–153)
CRP, mg/dL	0.65 (0.38–1.17)	0.64 (0.39–1.23)	0.82 (0.50–1.05)

Data are expressed as median, with IQR in parentheses. Comparison between populations was performed by ANOVA test and χ^2 test.

Significant differences between adequately treated and undertreated or overtreated group are expressed as:

[a] $P < 0.0001$.

[b] $P < 0.05$.

[c] $P < 0.001$.

[d] $P < 0.01$.

Significant differences between undertreated and overtreated group are expressed as:

[aa] $P < 0.05$.

[bb] $P < 0.0001$.

[cc] $P < 0.01$.

[dd] $P < 0.001$.

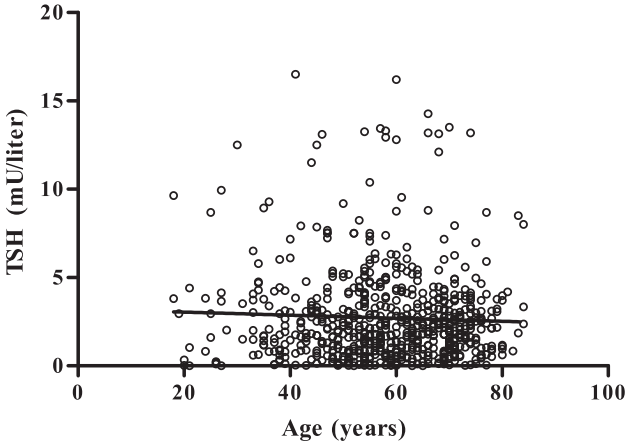

Figure 1. Correlation between serum TSH levels and age in obese LT4 users.

Correlation and regression analyses in obese LT4 users

Bivariate correlation analysis showed that the daily LT4 dose was associated with many bodily variables, although FFM was the strongest correlate (Table 4). In a model including age, sex, cause of hypothyroidism, diabetes mellitus, %FM and FFM, as well as duration of LT4 treatment, a stepwise multivariable regression analysis documented that daily LT4 microgram per kilogram dose was best predicted by FFM ($\beta = 0.262$, $P < 0.0001$), total thyroidectomy ($\beta = 0.225$, $P < 0.0001$), and sex ($\beta = -0.122$, $P < 0.05$). In multinomial logistic regression analysis, the likelihood of LT4 overreplacement was associated with younger age, higher daily LT4 microgram per kilogram dose and lower BMI (Table 5). In contrast, the risk of underreplacement was only associated with male sex ($P < 0.05$).

Comparison with an euthyroid obese population

To test for potential anthropometric and metabolic effects relating to LT4 treatment in the obese setting, a comparably obese group of age-, sex-, and BMI-matched euthyroid subjects was enrolled among inpatients regularly admitted to our unit for obesity workup during the study period. In this group, BMI was >40 kg/m^2 in 77.6%, > 35.0 to 39.9 kg/m^2 in 16%, and >30.0 to 34.9 kg/m^2 in 6.4% of cases. None had inflammatory conditions and CRP levels were similar between populations. Despite having comparable BMIs, groups differed in terms of %FM and, insignificantly, FFM. Nevertheless, FFM-adjusted REE was higher in LT4 users than euthyroid controls. There was no between-group difference in glucose and insulin levels, hence insulin resistance. Conversely, LT4 users exhibited a healthier lipid profile because of lower total and LDL-cholesterol levels than euthyroid controls. These differences remained unchanged after excluding the subgroup of over- and underreplaced patients from the LT4 group.

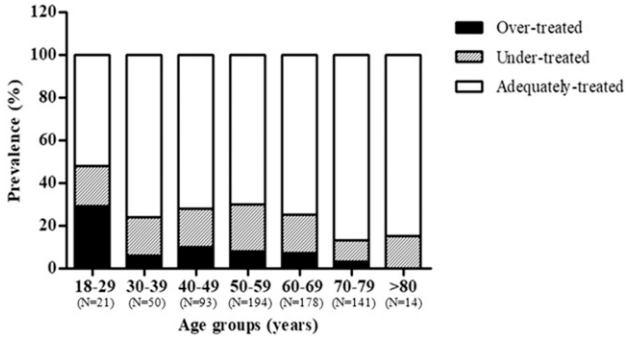

Figure 2. Prevalence of obese LT4 users with low TSH (overtreated), euthyroid (adequately treated), and high TSH (undertreated) subdivided according to the age decades. For each decade, proportions are expressed as percent values and the number of subjects is displayed in parentheses on the horizontal axis.

Discussion

LT4 represents the first-line replacement treatment in primary hypothyroid patients with the aim to restore normal TSH secretion, promote patients' well-being, and reduce the systemic consequences of hypothyroidism (14). Studies in the general population reported a variably high proportion of patients with abnormal TSH during replacement therapy with LT4, even in the case of frequent monitoring for dosing adjustments. In the Colorado Thyroid Study, abnormal TSH levels were documented in 40% of 1525 patients taking thyroid medications, with more than one-fifth of cases showing low TSH values (25). A UK survey on 1037 patients noted abnormal thyroid function testing in 37.2% of cases, with 17.4% being overtreated and 19.8% being undertreated (26). Furthermore, in 29.5% of 266 LT4 users from the Pomerania study TSH levels were outside the reference range, and again more patients were overreplaced than underreplaced, namely 19.5% vs 10% of cases (27). Our analysis on obese individuals with primary hypothyroidism evaluated the prevalence of adequate LT4 treatment and attempted to gain insights on factors relating to abnormal thyroid testing in this cohort. Results highlight a peculiar role for obesity on LT4 requirements, with nearly 75% of participants showing TSH levels within the euthyroid range. Among those with abnormal TSH, the rate of LT4 underreplacement predominated compared with that of overreplacement, namely 17.2% vs 7.5% of cases. The reason for this outcome remains unclear. Current general recommendations toward specialized management of obesity increase the chance of stricter follow-ups (36), thus our finding could simply be the result of improved obesity management. Alternatively, several studies have

Table 3. Summary of Anthropometric and Thyroid Function Data Obtained in Obese LT4 Users Divided According to Age <65 and ≥65 Years

Variables	Patients Aged <65 y (n = 453)	Patients Aged ≥65 y (n = 238)	*P*
Males/females, N, %	55/397 (12.1/87.9)	31/207 (13/87)	0.7
Age, y	54 (45–58)	71 (69–74)	<0.0001
BMI, kg/m^2	44.3 (40.3–49.4)	43.2 (39.7–47.2)	<0.01
FM, %	50.1 (45.9–53.5)	52.4 (48.0–55.4)	<0.0001
FFM, kg	55.3 (50.7–61.6)	49.5 (45.5–56.5)	<0.0001
LT4 dose, μg/d	100 (75–132)	100 (50–125)	<0.0001
LT4 dose, μg/kg/d	0.93 (0.66–1.18)	0.88 (0.55–1.14)	<0.05
TSH, mU/L	1.99 (0.88–3.83)	2.14 (1.10–3.26)	0.3
FT4, ng/L	11.9 (10.8–13.6)	12.3 (10.9–13.7)	0.5
CRP, mg/dL	0.7 (0.4–1.3)	0.5 (0.3–1)	<0.001
Adequately treated, %	319 (70.6%)	200 (84.0%)	<0.05
Undertreated, %	92 (20.4%)	38 (16.0%)	0.2
Overtreated, %	41 (9.1%)	11 (4.6%)	<0.05

Data are expressed as median, with IQR in parentheses, or as percentage. Comparison between populations was performed by ANOVA and χ^2 test.

shown that BW is maintained in a stable range, known as the set-point, despite the variability in energy intake and expenditure (37). This regulatory physiology is largely governed by leptin, a known hypothalamic modulator of TRH secretion, which could act to cushion TSH variations in obese patients until a new metabolic set-point develops, such as that generated by weight loss obtained during an inpatient regimen (33) or after bariatric surgery (38). Because of the cross-sectionality of this study, the aptness of our interpretation remains to be verified in prospective studies achieving adequate variations in metabolic set-point.

Table 4. Bivariate Correlation Analysis Between the Daily LT4 and LT4 μg/kg Dose and Anthropometric or Metabolic Variables in LT4 Users

Variables	LT4/d	LT4 μg/kg/d
Sex	0.04	−0.05
Age, y	**−0.15**[a]	−0.05
BMI, kg/m^2	**0.09**[b]	**−0.19**[a]
WC, cm	**0.11**[b]	**0.16**[c]
FM, %	−0.003	**−0.12**[d]
FFM, kg	**0.19**[a]	**−0.11**[d]
REE, kcal/d	**0.14**[d]	**−0.11**[b]
REE_{FFM}	0.02	0.04
TSH, mU/L	**−0.13**[a]	**−0.20**[a]
FT4, ng/L)	**0.24**[a]	**0.28**[a]
Glucose, mg/dL	0.02	0.01
Insulin, mU/L	−0.02	−0.07
HOMA-IR	−0.01	−0.05
CHO, mg/dL	−0.04	−0.03
LDL-CHO, mg/dL	−0.01	−0.01
HDL-CHO, mg/dL	−0.06	−0.02
TG, mg/dL	−0.01	−0.01

Significant correlations are shown in bold.

For significance:

[a] $P < 0.0001$.

[b] $P < 0.05$.

[c] $P < 0.001$.

[d] $P < 0.01$.

TSH was unrelated to age but aging was associated with an improving rate of euthyroid TSH levels. We observed that median dose of LT4 microgram per kilogram BW decreased with age, a finding that corroborates previous studies and, in this cohort, is potentially linked to underlying sarcopenic obesity. In older people, inflammatory conditions or nonthyroidal illness could *per se* alter TSH and FT4 adequacy to assess genuine euthyroidism, whereas 3,5,3′-triiodothyronine (FT3) measurement can improve results accuracy (39). Because we did not measure FT3 levels, the potential influence of extrathyroidal conditions on our results cannot be discriminated. However, acute illness and/or inflammation was verified upon clinical assessment and by measurement of CRP levels at study entry to avoid including potential cases. Of note, the prevalence of overtreatment, a matter of concern for cardiac and skeletal health in the elderly, decreased with age and totaled 5% in patients aged ≥65 years. This figure differs from data reported in the Cardiovascular Heart Study (13) and the Framingham Heart Study (40), in which overtreatment rates in the elderly were 41% and 43%, respectively, whereas it overlaps with that obtained in an endocrine clinic population (41). The discrepancy could be explained by the circumstance that our referral center may admit patients undergoing endocrine surveillance elsewhere. Thus, we cannot dismiss the possibility of overappraisal of LT4 treatment adequacy in this subgroup. Although endorsing current recommendations on adequate thyroid function monitoring in older LT4 users (12, 14), the apparent favorable outcome observed in our elderly cohort should be interpreted with caution, based on the evidence that target TSH levels during LT4 treatment should be age-adjusted to avoid the risk of overtreatment in the elderly (12, 14).

Table 5. ORs for LT4 Overtreatment and Undertreatment vs Adequate Treatment

	LT4 Overtreatment		LT4 Undertreatment	
Covariates	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Age	**0.96 (0.94–0.99)**	**0.001**	0.99 (0.97–1.01)	0.2
Sex				
Female	1	Ref.	1	Ref.
Male	1.75 (0.55–5.59)	0.3	**2.37 (1.10–5.11)**	**0.03**
BMI	**0.93 (0.88–0.99)**	**0.01**	1.01 (0.98–1.05)	0.5
LT4 dose, μg/kg/d	**2.98 (1.44–6.14)**	**0.003**	1.02 (0.59–1.78)	0.9
Duration of hypothyroidism	0.99 (0.95–1.04)	0.8	0.99 (0.96–1.02)	0.5
FFM, kg	0.98 (0.95–1.02)	0.3	1.01 (0.99–1.04)	0.3
Cause of hypothyroidism				
AITD (0)	1	Ref.	1	Ref.
Thyroidectomy (1)	1.38 (0.58–3.25)	0.5	0.56 (0.29–1.27)	0.2
Presence of diabetes mellitus				
No (0)	1	Ref.	1	Ref.
Yes (1)	1.30 (0.45–3.22)	0.7	0.47 (0.40–1.55)	0.5

Significant correlations are shown in bold.

Abbreviation: Ref., reference value.

In terms of LT4 requirement, the median LT4 dose was 0.91 μg/kg/d. BW is a good indicator for calculating an appropriate starting dose of LT4, with other determinants including age, sex, body composition, cause and validation of hypothyroidism, as well as comorbidities, drugs, and adherence to therapy (4–11, 14, 42, 43). Notwithstanding the suggestion that severe obesity may require higher than normal LT4 doses because of impaired LT4 pharmacokinetics and T4 to T3 conversion (31), we failed to observe apparent defects in LT4 absorption in this large obese group and confirmed earlier evidence showing that the weight-adjusted LT4 dose decreases with increasing BMI (44, 45). Moreover, our findings on FFM confirm that lean mass exerts a predictive role on LT4 dose (38, 44), which has been linked to cellular processes of deiodination and thyroid hormone metabolism taking place in muscle cells (46).

In the search for factors potentially associated with abnormal thyroid function testing, the role of anthropometric and metabolic variables of LT4 users was explored according to patients' TSH. Patients with low TSH were younger, took a higher LT4 dose, and exhibited a poorer lean mass relatively to body mass compared with those with euthyroid TSH values. On the other hand, patients with high TSH levels also were younger and were more frequently males, more abdominally obese, and their LT4 dose appeared disproportionately low relative to their lean mass. REE normalized by FFM appeared to decrease across categories of LT4 users with low to high TSH. This result substantiates the concept that thyroid hormone and thyrotoxicosis exerts stimulatory effects on protein metabolism, heat production and metabolic efficiency (1). Likewise, a recent six-month interventional study by Samuels *et al.* (47), although failing to document a direct effect of LT4 dose modifications on REE normalized for lean body mass, noticed that its increases correlated directly with increases in FT4 and FT3 levels and inversely with increases in TSH levels across the achieved range of TSH levels. At odds with findings obtained in the general population on the favorable effect of LT4 replacement on the lipid profile (18–22), we could document only modest decrements of total and LDL-cholesterol along with declining levels of serum TSH in LT4 users. In terms of glucose homeostasis, the high TSH subgroup harbored substantially higher insulin resistance and insubstantially higher glucose levels compared with the other subgroups. Previous studies informed on associations between insulin resistance and thyroid function summarized as follows: (i) a cross-sectional association exists between insulin resistance and TSH levels (48); (ii) the hypothyroid state is linked to a cellular condition of insulin resistance in adipocytes and muscle cells (49, 50); and (iii) treatment of hypothyroidism improves insulin resistance (51). Although these and our findings pinpoint the potential link between LT4 adequacy and insulin resistance, we found that neither diabetes mellitus nor metformin treatment altered the risk of thyroid testing abnormalities. This lack of result adds argument to the ongoing debate on the relation between diabetes mellitus and the risk of LT4 overtreatment in the general population, in which both positive (13) and negative (26) associations have been identified. With reference to the risk of abnormal thyroid testing, logistic regression analysis showed that the likelihood of overtreatment was associated with younger age, higher LT4 dose, and lower BMI, whereas only male sex increased

the risk of LT4 undertreatment. These results corroborate those of studies in nonobese populations, reporting a relation between LT4 dose and overtreatment risk on one side, and between male sex and undertreatment risk on the other (13, 52). Together, our results suggest that the adequacy of treatment in obesity is potentially associated with anthropometric and metabolic outcomes and underscore the role of lean mass and age in regulating LT4 requirements. Whether this implies that assessment of body composition may help in titrating individual L-T requirements remains to be demonstrated.

To implement our understanding of residual metabolic risks in obese subjects on LT4, their metabolic profile was examined in comparison with an equally obese group of euthyroid controls. Despite the similarities in BMI distribution, adiposity was higher in LT4 users than in euthyroid obese controls, which agrees with previous evidence that hypothyroid patients only experience modest reductions in fat mass (1). Moreover, ~15% of LT4-treated subjects do not reach clinical euthyroidism (14) as a result of impaired intracellular T3 production determined by the downregulation of the deiodinase pathway (53). Hypothetically, the existence of underlying peripheral hypothyroidism may ultimately influence long-term regulation of body composition and contribute to explain current observations. Nonetheless, the levels of total CHO and LDL-cholesterol were lower in LT4-treated than in euthyroid controls, without differences in HDL-cholesterol and TG levels. These findings are in line with those of previous randomized crossover (19, 23), double-blind placebo-controlled (20, 21), and longitudinal studies (22) investigating on LT4 effects on lipids in nonobese populations (19–23). Current results also agree with those of a meta-analysis showing a decreasing effect of LT4 replacement on total and LDL-cholesterol in LT4 users, while HDL-cholesterol and TG levels remained unaltered (54). Conversely, a meta-analysis of 99 studies documented persistently higher total and LDL cholesterol levels were observed in LT4 users compared with controls (24). Because of the lack of studies on lipids in LT4-treated obese populations (55), we cannot draw conclusive clinical implications from our results.

Our study depicts a real-world snapshot of LT4 therapy in hypothyroid obesity. As such, it has a number of limitations, such as the cross-sectional design, the lack of FT3 measurement, and information on therapeutic adherence (56–59). As individual adequacy of LT4 therapy was based on the incidental finding of normal TSH, this measure may inadequately reflect the long-term thyroid hormone replenishment status of these patients. Furthermore, this study did not include a group of lean hypothyroid LT4 users to compare rates of inadequate LT4 replacement in the general population. Rather, our study aim was to discriminate the effect of LT4 on the metabolic phenotype of obesity. The strength of the clinical information originating from our investigation includes a lower than expected rate of inadequate LT4 replacement, an improving LT4 adequacy with aging, and a relation between LT4 requirement and sex, age, and lean body mass in this obese cohort. Although our results imply that a limited proportion of LT4 users is overtreated among obese patients referring to an obesity clinic, current data also support the recommendation that TSH target during LT4 replacement should be age adjusted, and LT4 adequacy should be especially monitored in elderly obese individuals to avoid the detrimental effect of overtreatment.

Acknowledgments

Financial Support: This study was partially funded by the AGING Project for Department of Excellence at the Department of Translational Medicine (DIMET), Università del Piemonte Orientale, Novara, Italy.

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Disclosure Summary: The authors have nothing to disclose.

Data Availability: All data generated or analyzed during this study are included in this published article or in the data repositories listed in References.

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