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# Effects of Levothyroxine Replacement or Suppressive Therapy on Energy Expenditure and Body Composition

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***Background:*** Thyrotropin (TSH)-suppressive doses of levothyroxine (LT4) have adverse effects on bone and cardiac function, but it is unclear whether metabolic function is also affected. The objective of this study was to determine whether women receiving TSH-suppressive LT4 doses have alterations in energy expenditure or body composition.

***Methods:*** This study was a cross-sectional comparison between three groups of women: 26 women receiving chronic TSH-suppressive LT4 doses, 80 women receiving chronic replacement LT4 doses, and 16 untreated euthyroid control women. Subjects underwent measurements of resting energy expenditure (REE), substrate oxidation, and thermic effect of food by indirect calorimetry; physical activity energy expenditure by accelerometer; caloric intake by 24-hour diet recall; and body composition by dual X-ray absorptiometry.

***Results:*** REE per kilogram lean body mass in the LT4 euthyroid women was 6% lower than that of the LT4-suppressed group, and 4% lower than that of the healthy control group ($p = 0.04$). Free triiodothyronine (fT3) levels were directly correlated with REE, and were 10% lower in the LT4 euthyroid women compared with the other two groups ($p = 0.007$). The groups of subjects did not differ in other measures of energy expenditure, caloric intake, or body composition.

***Conclusions:*** LT4 suppression therapy does not adversely affect energy expenditure or body composition in women. However, LT4 replacement therapy is associated with a lower REE, despite TSH levels within the reference range. This may be due to lower fT3 levels, suggesting relative tissue hypothyroidism may contribute to impaired energy expenditure in LT4 therapy.

## Introduction

Levothyroxine (LT4) doses that suppress serum thyrotropin (TSH) levels are used to prevent growth of thyroid cancer and, less commonly, thyroid nodules. However, LT4 suppressive therapy may have adverse effects on target organs, particularly the heart and bones. For this reason, recommendations regarding optimal LT4 doses in these conditions have become less aggressive (1).

LT4 suppression therapy may also affect metabolic function, since thyroid hormone plays a critical role in determining energy expenditure, body mass, and body composition (2). A number of studies have investigated effects of supraphysiologic thyroid hormone doses on metabolism, but most have been short-term studies (3–14 days) of healthy subjects (3–7). These studies uniformly showed increased resting and 24-hour energy expenditure, but were too brief to document changes in body composition. In addition, most utilized high doses of levotriiodothyronine (LT3), not minimally suppressive doses of LT4.

Only a handful of studies have reported the metabolic effects of long-term LT4 suppression therapy (8–12). While significant changes in resting energy expenditure (REE) were not found, some did demonstrate effects on body weight or composition. None investigated other components of energy balance, including food intake, physical activity, or the thermic effect of food (TEF).

The current study compared effects of chronic LT4 suppressive therapy on energy balance and body composition in women to two matched groups of euthyroid women either receiving replacement doses of LT4, or with no history of thyroid disease. Sensitive measures of food intake, energy expenditure components, physical activity, and body composition were employed to develop a metabolic phenotype of

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patients receiving chronic suppressive LT4 therapy. It was hypothesized that subjects receiving suppressive doses of LT4 would have increased food intake, REE, lipid oxidation, physical activity energy expenditure, and TEF compared with healthy subjects and those receiving replacement doses of LT4. Further, it was hypothesized that these changes would result in altered body composition, with decreased lean body mass and fat mass.

## Materials and Methods

### *Experimental subjects*

All qualifying LT4-suppressed subjects in the authors' thyroid clinics were approached to ascertain their interest in enrolling in the study. Twenty-six agreed to participate and are represented in this report. The LT4 euthyroid and healthy control subjects were recruited as part of a larger, ongoing thyroid study, and were chosen to match the LT4-suppressed subjects by age and menstrual status. This determined the number of subjects in these two groups. No subjects had any other acute or chronic illnesses or were on medications that affect thyroid hormone levels, appetite, metabolic function, or weight. Stable doses of oral contraceptive therapy were allowed. Testing was done during the first 14 days after onset of menstrual bleeding or an oral contraceptive cycle. Three groups of women were recruited: (i) LT4-suppressed group, (ii) LT4 euthyroid group, and (iii) healthy control group.

LT4-suppressed group. Twenty-six women (aged 23–54 years) receiving LT4 with low or undetectable TSH levels and normal or minimally elevated free thyroxine (fT4) levels were recruited from the OHSU Endocrinology Clinics. Sixteen of these subjects had a history of low-risk well-differentiated thyroid cancer, and were intentionally treated with TSH-suppressive LT4 doses, while 10 were unintentionally over-treated with LT4 for benign disease (hypothyroidism following therapy for Graves' disease in five patients and primary hypothyroidism in five patients). All subjects were diagnosed as adults, and all thyroid cancer patients had undergone total thyroidectomy and radioactive iodine ablation at least one year prior to study. Subjects had received LT4 therapy for 1–25 years ($M = 6.4$ years), and had been on stable LT4 doses for at least three months prior to study entry. Thyroid cancer patients had no evidence of disease based on recent monitoring with thyroglobulin levels and neck ultrasound.

LT4 euthyroid group. This group comprised 80 women (aged 21–54 years) receiving LT4 for primary hypothyroidism ($n = 62$), primary hypothyroidism plus lobectomy for benign disease ($n = 4$), hypothyroidism following $^{131}I$ therapy for Graves' disease ($n = 9$), postpartum thyroiditis leading to permanent hypothyroidism ($n = 3$), or history of thyroidectomy for nodular goiter or very low-risk differentiated thyroid cancer (DTC; $n = 2$). All subjects were diagnosed as adults with documented elevated TSH levels, and had received LT4 therapy for 0.4–35 years ($M = 10.2$ years), and had been on stable LT4 doses for at least three months prior to study entry.

Healthy control group. This group comprised 16 healthy women (aged 21–54 years) with no history of thyroid disease and normal TSH levels.

### *Experimental design*

The protocol was approved by the OHSU Institutional Review Board, and subjects gave written informed consent prior to enrollment.

Subjects were screened for general health, medicines, and thyroid status by history, physical examination, and laboratory testing. Within six weeks of screening, subjects returned for a single testing visit. Subjects refrained from taking LT4 that morning. Serum TSH, fT4, and free triiodothyronine (fT3) levels were obtained between 7am and 9am. Measures of energy balance and body composition were done:

Anthropometric measurements. Weight was measured with a digital scale (Model 5002; Scale-Tronix, Wheaton, IL) while wearing a hospital gown to the nearest 0.01 kg. Height was measured without shoes using a wall-mounted stadiometer (Harpenden Stadiometer, Holtain Ltd, Crymych, United Kingdom).

REE by indirect calorimetry. Indirect calorimetry was performed in a thermo-neutral room maintained at 21.1°C using a VMax Encore 29N Indirect Calorimeter (SensorMedics Viasys Healthcare, Yorba Linda, CA). This procedure was conducted after the participant fasted for 12 hours and before she performed any significant physical activity. Each subject initially rested comfortably on a bed for 20 minutes. A clear Plexiglas™ canopy was then fitted over her head and upper chest. Expired air was sampled and analyzed for the volume of oxygen consumed ($VO_2$) and carbon dioxide produced ($VCO_2$) each minute for 30 minutes. Variation of the analyzers was $<\pm 1\%$ in the range 0–100% $O_2$ and $CO_2$. REE was calculated using the modified Weir equation (13). Specific macronutrient oxidation was estimated by measuring 24-hour urine urea nitrogen (UUN), and estimating grams of carbohydrate, lipid, and protein oxidation using the equations of Jequier (14).

TEF. TEF was determined by indirect calorimetry immediately after REE was measured (15). Each participant consumed a standard liquid meal (Ensure; Ross Laboratories, Seattle, WA) that provided an energy intake of 35% of their REE. The macronutrient composition of the meal was 14% protein, 31.5% fat, and 54.5% carbohydrate. Post-prandial energy expenditure was measured for 15 minutes every half an hour for six hours using the procedure described for REE. For each 15-minute interval, the difference between TEF and the REE measurement was calculated. The six-hour area under the curve was calculated by the trapezoidal method. The TEF was then multiplied by 3.5, a constant that represents the typical consumption of three meals and one snack per day to estimate the total TEF in a 24-hour period.

Body composition by dual energy X-ray absorptiometry. Body composition was measured by dual energy X-ray absorptiometry (DEXA) using a Hologic QDR Discovery A Densitometer (Hologic, Inc., Bedford, MA) following standard procedures.

Diet intake. Three 24-hour food recall interviews were conducted by telephone within one week of the testing visit. The interviews were based on the standardized, computer-based Nutrition Data System for Research (NDSR), and were conducted by trained bionutritionists (16).

Physical activity. Physical activity was measured by the omnidirectional Actical® accelerometer (Philips Respironics, Bend, OR). Participants wore the accelerometer at the waist during waking hours for seven consecutive days within two weeks of the testing visit. Recorded data included activity counts; average activity (counts per minute); time interval duration (minutes); activity intensity ranges during sedentary, light, moderate, and vigorous activity; and accumulated time within each activity range (minutes).

### *Analytic methods*

TSH was measured by ICMA (Beckman Coulter, Brea, CA): functional sensitivity 0.02 mIU/L (reference range 0.34–5.60 mIU/L), intra-assay CV 9.5% at 0.03 mIU/L and 4.7% at 11.6 mIU/L, and inter-assay CV 11% at 0.04 mIU/L, 5% at 0.70 mIU/L, and 5.8% at 24.94 mIU/L. fT4 was measured by direct equilibrium dialysis (Nichols Institute, San Juan Capistrano, CA): sensitivity 0.08 ng/dL (reference range 0.8–2.7 ng/dL), intra-assay CV 5.7% at 0.27 ng/dL and 1% at 4.6 ng/dL, and inter-assay CV 6.8% at 0.3 ng/dL and 1.6% at 3.8 ng/dL. fT3 was measured by tracer dialysis (Nichols Institute): sensitivity 25 pg/dL (reference range 210–440 pg/dL), intra-assay CV 6%, and interassay CV 4%. UUN was measured in a 24-hour urine sample obtained within one week of the testing visit by hydrolysis (QuantiChrom kit; BioAssay Systems, Hayward, CA): functional sensitivity 0.08 mg/dL, intra-assay CV 2.6%, and inter-assay CV 5% at 950 mg/dL.

### *Statistical methods*

Related measures were analyzed together using linear models for repeated measures (Proc Mixed, SAS/STAT®). This methodology allows for correlation between measures for each subject. An unstructured covariance approach was used, which allowed for unequal variances for related measures and also separate variance covariance matrices for individuals in different groups. A few measures were analyzed individually. For these, again, allowance was made for different groups to have different variances. All models included adjustments for age and estrogen status. In addition, adjustments for lean body mass, percent fat, and meal size were included in the analyses of TEF variables.

To limit the effect of multiple comparisons, two assessments were made prior to conducting pairwise comparisons between groups: An initial assessment of whether there was evidence of a difference among groups for any of the related measures was obtained. Comparisons were then conducted between groups separately for each measure if the first overall *p*-value was <0.15. Finally, pairwise comparisons of groups for individual measures (or comparisons of groups with just a single measure in model) were conducted only if evidence of a group effect was observed at a significance level of 0.05. Natural logarithmic transformation was used for skewed outcomes.

For outcomes that were significantly different between groups (at 0.05), the study also assessed, with the groups combined, whether TSH, fT3, or fT4 were associated with the outcomes using regression models adjusting for the same covariates as in the main analyses. To assess the relationship between TSH and these outcomes, an analysis of the LT4-suppressed group was conducted separately, since TSH levels were markedly different for this group.

## Results

### *Clinical parameters and thyroid function tests*

The clinical parameters and thyroid function tests for the three groups are shown in Table 1. The groups were well

Table 1. Clinical Parameters and Thyroid Function Tests in the Three Groups

| | *Healthy controls* (N = *16*) | *LT4 euthyroid* (N = *80*) | *LT4 suppressed* (N = *26*) | p-*Values for comparing groups* |
|---|---|---|---|---|
| Age (years) | 39.6 ± 2.8 | 41.6 ± 0.9 | 39.3 ± 1.8 | 0.45 |
| BMI (kg/m$^2$) | 27.5 ± 1.9 | 27.3 ± 0.7 | 25.2 ± 0.9 | 0.32 |
| Estrogen status | 63% Pre-none<br>19% Pre-on<br>19% Post-none | 68% Pre-none<br>15% Pre-on<br>18% Post-none | 69% Pre-none<br>15% Pre-on<br>15% Post-none | 0.99 |
| Systolic blood pressure (mmHg) | 118 ± 4 | 114 ± 2 | 116 ± 4 | 0.72 |
| Diastolic blood pressure (mmHg) | 68 ± 2 | 67 ± 1 | 69 ± 3 | |
| Heart rate (beats/min) | 74 ± 3 | 71 ± 1 | 70 ± 3 | 0.68 |
| LT4 dose ($\mu$g/kg) | NA | 1.50 ± 0.07 | 1.92 ± 0.10[c] | <0.0001 |
| TSH ($\mu$/L) | 2.13 ± 0.22 | 2.08 ± 0.14 | 0.14 ± 0.02[a,c] | <0.0001 |
| fT4 (ng/dL) | 1.41 ± 0.07 | 1.63 ± 0.04[a] | 2.27 ± 0.09[a,c] | <0.0001 |
| fT3 (pg/dL) | 240 ± 11 | 216 ± 5[b] | 238 ± 7[d] | 0.007 |

Values shown are mean ± standard error of the mean, unless otherwise indicated.
[a]Significantly different from healthy control group at ≤0.02 by *post hoc* tests.
[b]Significantly different from healthy control group at ≤0.04 by *post hoc* tests.
[c]Significantly different from LT4 euthyroid group at ≤0.01 by *post hoc* tests.
[d]Significantly different from LT4 euthyroid group at ≤0.005 by *post hoc* tests.
BMI, body mass index; Pre-none, premenopausal, no hormone treatment; Pre-on, premenopausal on hormone treatment; Post-none, postmenopausal, no hormone treatment; LT4, levothyroxine; TSH, thyrotropin; fT4, free thyroxine; fT3, free triiodothyronine.

matched for age and estrogen status, and hence unadjusted and adjusted analyses are similar. Body mass index (BMI), blood pressure, and heart rate were not different among the groups. As expected, LT4-suppressed subjects were taking higher LT4 doses than LT4 euthyroid subjects were (1.50 ± 0.07 vs. 1.92 ± 0.10 μg/kg/day). Mean TSH levels were similar in the healthy control and LT4 euthyroid groups (2.13 ± 0.22 and 2.08 ± 0.14 mIU/L), and as expected were lower in the LT4-suppressed group (0.14 ± 0.02 mIU/L). TSH levels were not significantly different at the baseline visit compared to levels over the previous three months, including at the screening visit (data not shown). Within the LT4-suppressed group, TSH levels were <0.1 mIU/L in 10 subjects, and were between 0.1 and 0.33 mIU/L in 16 subjects. Compared with the healthy control group, mean fT4 levels were higher in the LT4 euthyroid group, and were even higher in the LT4-suppressed group (1.41 ± 0.07, 1.63 ± 0.04, and 2.27 ± 0.09 ng/dL). Mean fT4 levels were 2.44 ± 0.16 ng/dL in the 10 subjects with TSH levels of <0.1 mIU/L, and 2.17 ± 0.10 ng/dL in the 16 subjects with TSH levels of 0.1–0.33 mIU/L ($p$ = n.s.). Four LT4-suppressed subjects had slightly elevated fT4 levels (2.9, 2.9, 3.1, and 3.3 ng/dL) due to requirements for TSH suppression, while the other 22 LT4-suppressed subjects had normal fT4 levels. None of the control or LT4 euthyroid subjects had elevated fT4 levels. Mean fT3 levels were lower in the LT4 euthyroid group compared with the other two groups (216 ± 5 vs. 240 ± 11 and 238 ± 7 pg/dL). Mean fT3 levels were 248 ± 13 pg/dL in the 10 subjects with TSH levels of <0.1 mIU/L, and 231 ± 8 pg/dL in the 16 subjects with TSH levels of 0.1–0.33 mIU/L ($p$ = n.s.). fT3 levels were slightly below the reference range in four of the healthy control subjects, 41 of the LT4 euthyroid subjects, and five of the LT4-suppressed subjects. None of the subjects had an elevated fT3 level.

### *Energy expenditure and body composition*

Energy expenditure and body composition is shown in Table 2. REE was 6% lower in the LT4-replaced compared with the LT4-suppressed group (1302 ± 20 vs. 1376 ± 48 kcal/day), and was 4% lower in the LT4-replaced compared with the healthy control group (1302 ± 20 vs. 1354 ± 50 kcal/day), although this did not reach statistical significance ($p$ = 0.13). LT4-suppressed and healthy control subjects had similar REE levels ($p$ = 0.68). Significant differences were seen for REE corrected for lean body mass (30.2 ± 0.7 kcal/kg/day in controls, 28.9 ± 0.3 in LT4 euthyroid, and 30.7 ± 0.8 in LT4-suppressed groups; $p$ = 0.03 for difference between the LT4 euthyroid and the other two groups). REE (REE/kg) was positively correlated with serum fT3 levels ($p$ = 0.03), but not with fT4 or TSH levels. There were no differences in substrate oxidation rates, TEF parameters (total daily TEF, peak TEF, time to peak TEF), or body composition (lean body mass, fat mass, % fat mass) between the three groups.

### *Diet intake and physical activity*

Table 3 shows diet intake and physical activity. There were no differences in dietary intake measures between the three groups, including total daily caloric intake or percent intake of carbohydrates, fats, or protein. There were no differences in physical activity measures between the three groups, including total daily physical activity energy expenditure, or

Table 2. Energy Expenditure and Body Composition in the Three Groups

| *Measure* | *Healthy controls (N = 16)* | *LT4 euthyroid (N = 80)* | *LT4 suppressed (N = 26)* | p-*Values for comparing groups for set of outcomes* | p-*Values for comparing groups for individual outcomes** |
|---|---|---|---|---|---|
| REE (kcal/day) | 1354 ± 50 | 1302 ± 20 | 1376 ± 48 | 0.13 | 0.38 |
| REE/LBM (kcal/kg/day) | 30.2 ± 0.7 | 28.9 ± 0.3 | 30.7 ± 0.8[a] | | 0.04 |
| CHO oxidation (g/day) | 119 ± 13 | 134 ± 6 | 142 ± 12 | 0.55 | |
| Fat oxidation (g/day) | 70 ± 6 | 56 ± 3 | 61 ± 4 | | |
| Protein oxidation (g/day) | 50 ± 4 | 53 ± 2 | 54 ± 3 | | |
| TEF (kcal/day) | 131 ± 13 | 142 ± 8 | 136 ± 13 | 0.21** | |
| TEF peak energy (kcal) | 34.3 ± 1.2 | 33.4 ± 0.7 | 34.3 ± 1.4 | 0.96 | |
| TEF time to peak (h) | 1.6 ± 0.3 | 1.8 ± 0.2 | 1.5 ± 0.3 | | |
| Lean body mass (kg) | 45.0 ± 1.8 | 45.3 ± 0.7 | 45.0 ± 1.5 | 0.92 | |
| Fat mass (kg) | 27.4 ± 3.9 | 25.9 ± 1.3 | 23.5 ± 1.5 | | |
| % fat mass | 34.5 ± 2.3 | 34.2 ± 0.9 | 32.7 ± 1.1 | 0.57 | |

Values shown are mean ± standard error of the mean, unless otherwise indicated.

REE values were available for all subjects.

Substrate oxidation values were available for 15 healthy controls, 78 LT4 euthyroid subjects, and 25 LT4-suppressed subjects due to missing 24-hour urine samples in the remaining subjects.

TEF values were available for all 16 healthy controls, 53 LT4 euthyroid subjects, and 24 LT4-suppressed subjects due to scheduling or technical limitations in the remaining subjects.

Body composition values were available for all subjects, except for one LT4-suppressed subject who declined the DEXA test.

Mixed models were adjusted for age and menstrual status. TEF was also adjusted for LBM, %fat, and meal size.

*Only obtained if $p$-value for comparing groups for set of outcomes was <0.15.

**TEF (kcal/day) analyzed separately from other TEF values due to lack of convergence in model including all three outcomes.

[a]Significantly different from LT4 euthyroid group at ≤0.03 by *post hoc* tests.

REE, resting energy expenditure; LBM, lean body mass; CHO, carbohydrate, TEF, thermic effect of food, calculated from 6-hour TEF area under the curve multiplied by 3.5 to estimate total daily TEF.

Table 3. Dietary Intake and Physical Activity in the Three Groups

| *Measure* | *Healthy controls (N = 16)* | *LT4 euthyroid (N = 80)* | *LT4 suppressed (N = 26)* | p-*Values for comparing groups* |
|---|---|---|---|---|
| Daily energy intake (kcal/kg/day) | 31.2 ± 2.8 | 26.8 ± 0.9 | 29.8 ± 2.8 | 0.23 |
| % CHO intake | 49.0 ± 1.8 | 46.4 ± 0.9 | 48.2 ± 1.8 | |
| % fat intake | 33.9 ± 1.4 | 35.4 ± 0.7 | 33.2 ± 1.6 | 0.65 |
| % protein intake | 14.4 ± 0.9 | 16.2 ± 0.3 | 16.1 ± 0.8 | |
| Total daily physical activity energy expenditure (kcal/day) | 712 ± 99 | 637 ± 34 | 622 ± 48 | 0.72 |
| Daily physical activity energy expenditure—light (kcal/day) | 186 ± 19 | 173 ± 7 | 169 ± 10 | |
| Daily physical activity energy expenditure—moderate/vigorous (kcal/day) | 526 ± 85 | 464 ± 31 | 453 ± 45 | 0.90 |
| Daily time spent in sedentary activities (min) | 454 ± 36 | 519 ± 13 | 496 ± 24 | |
| Daily time spent in light activities (min) | 225 ± 4 | 212 ± 6 | 221 ± 11 | |
| Daily time spent in moderate/vigorous activities (min) | 169 ± 22 | 150 ± 9 | 159 ± 16 | 0.61 |
| % Daily time spent in sedentary activities | 53.7 ± 1.9 | 58.8 ± 0.9 | 56.6 ± 1.8 | |
| % Daily time spent in light activities | 26.6 ± 1.7 | 24.1 ± 0.7 | 25.2 ± 1.2 | |
| % Daily time spent in moderate/vigorous activities | 19.7 ± 2.2 | 17.1 ± 1.0 | 18.2 ± 2.1 | 0.57 |

Values shown are mean ± standard error of the mean, unless otherwise indicated.

Mixed models were adjusted for age and menstrual status.

Diet intake values were available for all 16 healthy controls, 79 LT4 euthyroid subjects, and 25 LT4-suppressed subjects due to limitations in scheduling diet recalls.

Physical activity values were available for 15 healthy controls, 79 LT4 euthyroid subjects, and all 26 LT4-suppressed subjects due to technical limitations with an Actical device.

Daily physical activity energy expenditure for sedentary activities is not shown because the Actical software sets sedentary activities at zero energy expenditure.

Moderate and vigorous activity measures were combined because energy expenditure and percent time spent in vigorous activity were very low in all groups.

energy expenditure and time spent in sedentary, light, or moderate/vigorous activities.

## Discussion

The effects of LT4 suppressive therapy on energy expenditure, body composition, dietary intake, and physical activity levels in otherwise healthy women with benign thyroid conditions or low-risk thyroid cancer were investigated. Sensitive, validated measures were utilized to provide a ''metabolic phenotype'' of these subjects. Two carefully matched control groups were included: healthy euthyroid women on no LT4 therapy, and women with normal TSH levels on LT4 therapy for hypothyroidism.

It was hypothesized that LT4-suppressed women would have increased food intake, REE, lipid oxidation, physical activity energy expenditure, and TEF compared with the other two groups. It was also hypothesized that these alterations in energy economy would lead to changes in body composition. However, this was not the case, as LT4-suppressed women had similar metabolic parameters to healthy controls.

Past studies have reported increased resting or 24-hour energy expenditure and whole body oxygen consumption with exogenous administration of pharmacologic doses of LT4 or LT3 to healthy humans (3–7) due to increased expression of uncoupling proteins and decreased mitochondrial efficiency (3,4,7). Most of these studies were too short to record changes in body composition, although one 77-day study of high-dose LT3 reported decreased lean and fat mass in seven healthy men (6). These studies utilized doses of thyroid hormone that caused increases in thyroid hormones well above the physiologic range for short periods of time, and are not relevant for long-term therapy with lower doses of LT4.

More relevant are reports in patients with DTC treated for at least six months with lower but still suppressive doses of LT4. One study found no differences in REE or body composition compared to healthy controls (12), while the other found no change in lean body mass but a 9% decrease in muscle mass in the DTC group (9). A third study randomly assigned DTC patients to continue LT4 suppressive therapy versus lowering LT4 doses for six months, and found no changes in body composition, despite an increase in mean TSH levels from 0.07 to 4.35 mIU/L (8). The present findings extend these reports with more complete measurements of the ''metabolic phenotype'' in these patients, including substrate oxidation, TEF, dietary intake, and activity levels. Taken together, the current findings and past reports indicate that long-term, minimally suppressive doses of LT4 do not have major salutary or adverse effects on energy expenditure or body composition.

These data are in contrast to studies in endogenous subclinical hyperthyroidism, which have reported increased basal $VO_2$, decreased lean body mass, and increased percent body fat (17–19). Subjects in one study were given methimazole, and basal $VO_2$ normalized when they became euthyroid (17). These studies suggest that endogenous

subclinical hyperthyroidism, in contrast to exogenous LT4 suppressive therapy, may induce long-term alterations in energy expenditure and body composition. Serum T3 levels are higher in endogenous subclinical hyperthyroidism, which may explain the differing effects on metabolic function and body composition compared with exogenous LT4 suppression (20). In fact, fT3 levels in the LT4-suppressed group in the present study were indistinguishable from those in the healthy control group, which may protect LT4-suppressed patients from adverse metabolic effects seen in endogenous subclinical hyperthyroidism.

An unexpected finding was the lower REE/kg lean body mass observed in LT4 euthyroid women, which was 6% lower than in the LT4-suppressed group and 4% lower than in the healthy control group. In addition, it was confirmed that REE was positively correlated with fT3 levels across the three groups. Population-based studies in non-LT4-treated euthyroid subjects have reported that resting, sleeping, or 24-hour energy expenditure are directly correlated with free or total thyroid hormone levels (21–23), and that TSH is inversely correlated with basal oxygen consumption, a marker of energy expenditure (24). In two studies of energy expenditure in LT4-treated euthyroid subjects, REE increased as LT4 doses were adjusted to lower TSH levels within the reference range (25,26). Although not a prospective study, the present data represent the largest group of LT4-treated subjects studied using specific measures of energy expenditure and body composition to date, and the only study to compare LT4-treated euthyroid subjects with matched controls and LT4-suppressed subjects. In contrast to the REE findings, differences in TEF, substrate oxidation, dietary intake, or physical activity levels among subject groups could not be demonstrated.

Approximately half of the LT4 euthyroid subjects had fT3 levels below the reference range, despite mean TSH levels of 2.08 mIU/L. Low total or fT3 levels have been described in many LT4-treated euthyroid subjects (reviewed by Jonklaas *et al.*) (27), with one study showing that TSH levels below the reference range were needed to restore T3 levels to pre-surgery levels in patients after thyroidectomy (28). Two recent crossover studies randomized hypothyroid subjects on stable LT4 doses to continued LT4 therapy versus LT3 or desiccated thyroid extract, maintaining similar TSH levels within the reference range (29,30). Subjects lost 1.4 kg after 16 weeks of desiccated thyroid extract and 1.8 kg after six weeks of LT3, although there was no change in REE in the LT3 study (30). This raises the question of whether LT4-treated subjects with low T3 levels could benefit from low-dose LT3 therapy to assist with body weight regulation. However, all but one randomized controlled studies of combined LT4/LT3 in hypothyroid subjects failed to find any differences in weight between combined LT4/LT3 and LT4 monotherapy (31–39). In addition, REE was not affected in the study by Celi et al. (30). Therefore, further investigation of energy expenditure and LT3 effects in treated hypothyroidism is needed.

Despite lower REE, the LT4 euthyroid women had similar BMI and body composition compared to healthy controls and LT4-suppressed women. There is a large but inconclusive body of literature on the correlation between thyroid hormone levels and weight or body composition. Most population-based studies in healthy (non-LT4 treated) subjects have shown a direct correlation between serum TSH levels within the reference range and body weight, BMI, or fat mass (reviewed by Garin *et al.*) (40), suggesting a role for thyroid-inducible metabolism on body weight and composition. Longitudinal studies have been more divergent, with some but not all studies reporting a correlation between baseline TSH, fT4, or fT3 and weight gain over time (40–45). However, the correlations have been in different directions, and the point has been raised that weight change may affect thyroid hormone levels, rather than thyroid hormones affecting weight change (46).

Fewer studies have examined body weight and composition in LT4-treated subjects. None have shown significant differences in these parameters compared to control subjects (47,48) or when LT4 doses were altered to lower TSH within the reference range (14,41). These studies are concordant with the present results. However, one study did show greater one-year weight gain in LT4-treated subjects after thyroidectomy or with pre-existing hypothyroidism compared with euthyroid subjects (49). Subjects were well matched for age, sex, menopausal status, TSH levels, and baseline BMI. Compared with euthyroid controls, LT4-treated thyroidectomized subjects gained an excess of 1.8 kg over one year, and LT4-treated hypothyroid subjects gained an excess of 0.9 kg. The current findings cannot explain why a lower REE (as well as lower mean fT3 levels) in the LT4 euthyroid group did not translate to a higher BMI than the healthy control or LT4-suppressed groups. The numbers of subjects in the latter two groups were relatively small, raising the possibility that differences in mean BMI levels might become significant if the sample size had been larger. However, mean BMIs were 27.5 $kg/m^2$ in the healthy control group and 27.3 $kg/m^2$ in the LT4 euthyroid group, and it is difficult to argue that such a small difference would be significant with a larger sample size. It is possible that subtle compensatory changes in caloric intake or physical activity occurred that were not apparent in the current study to account for the lack of differences in BMI. In this regard, it would be interesting to measure total energy expenditure in free-living subjects with treated hypothyroidism, which was not done in the current study.

There are a number of strengths to this study, including the two well-matched control groups and sensitive measures of energy expenditure, body composition, diet intake, and physical activity. However, the study has limitations as well. The major limitation is its cross-sectional design at a single time point, which does not allow for determination of causality or trends over time.

A second major limitation is the heterogeneous nature of the two LT4-treated groups, which was necessitated by the practicalities of recruiting for an intensive clinical study. These two groups were heterogeneous in terms of underlying diagnosis, severity and duration of hypothyroidism, and LT4 dose requirements. LT4-treated subjects had received LT4 for variable time periods, and the mean duration of therapy was longer in the LT4 euthyroid group compared with the LT4-suppressed group. Most of the subjects had been on stable doses of LT4 for at least six months, but a few had minor dose adjustments three to six months prior to the study, which may not have been long enough for body composition effects to stabilize. However, a minimum of three months on a stable LT4 dose has been more than sufficient to observe changes in energy expenditure (31). Within the LT4-suppressed group, 10 subjects were inadvertently over-treated with LT4 for between four months and seven years, and therefore may have had less consistent

exposure to suppressed TSH levels than the subjects with thyroid cancer had. Among the subjects in the LT4-suppressed group, 10 had TSH levels <0.1 mIU/L, while 16 had TSH levels between 0.1 and 0.33 mIU/L. It is possible that greater levels of TSH suppression would have a more pronounced effect on metabolic parameters, although this may be less clinically relevant, as less aggressive LT4 suppressive therapy is now recommended for patients with thyroid cancer (1). The presence of residual thyroid tissue in some LT4 subjects may have led to some endogenous T3 production when compared with thyroidectomized subjects. The limited sample size did not allow for subgroup analysis of these variables, which would be important to investigate in the future.

A third limitation of the study is the relatively small numbers of subjects in the healthy control and LT4-suppressed groups, which were constrained by the available subjects from the larger study. This raises the possibility that there are true differences in one or more of the metabolic measures in the LT4-suppressed group, which were not found due to the limited sample size, although the magnitude of these differences would likely be small, given the data. Despite the relatively small sample size, significantly lower REE was found in the LT4 euthyroid group. While there is a relatively large number of comparisons for the number of subjects, this was accounted for by performing group analyses together, progressing to pairwise comparisons only in the presence of significant group effects and examining subscales only when there was evidence of interaction.

Subjects volunteered to participate in the study, and it is possible that subjects less satisfied with their weight or general health status may have preferentially volunteered, introducing a selection bias. An argument against this criticism is the fact that the LT4-treated euthyroid group had the same BMI and body composition as the other two groups had, despite the fact that these variables were not matched *a priori*. Finally, only women were studied, and it is not clear whether the findings would apply to men treated with LT4.

In summary, this is the most comprehensive study to date of energy expenditure, caloric intake, and body composition in women treated with LT4 at replacement or TSH-suppressive doses. It was found that LT4-suppressed subjects had similar measures of energy expenditure and body composition as healthy control subjects had, indicating that minimal LT4 suppression therapy does not produce adverse effects on metabolic function. On the other hand, LT4 euthyroid women had lower REE than LT4-suppressed women had, as well as a trend toward lower REE than healthy controls. This group also had lower mean fT3 levels, raising the intriguing possibility that low-dose LT3 therapy might benefit the metabolic profile of these women. However, this possibility requires further rigorous interventional studies of metabolic function in LT4-treated subjects to establish the long-term balance between benefits and the known risks of LT3.

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## Author Disclosure Statement

No competing financial interests exist for any of the authors.

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