Weight Loss after Therapy of Hypothyroidism Is Mainly Caused by Excretion of Excess Body Water Associated with Myxoedema

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Context: In hypothyroidism, resting energy expenditure (REE) is reduced and weight gain is common. Physical activity contributes to the total daily energy expenditure, and changes in physical activity might contribute to hypothyroid-associated weight changes.

Objective: The objective of the present study was to evaluate mechanisms involved in body weight changes associated with hypothyroidism.

Design, Setting, and Participants: We conducted a 1-yr controlled follow-up study on outpatients newly diagnosed with hypothyroidism (n = 12) and a euthyroid measurement control group (n = 10).

Main Outcome and Interventions: Changes in body mass and composition (dual-energy x-ray analysis scan), REE (indirect calorimetry), and spontaneous physical activity (pedometers and two different questionnaires) were studied before and after 12 months of L-T_4 therapy or observation (control group).

Results: TSH changed from 102 (85) to 2.2 (2.1) mU/liter mean (SD) and free T_4 from 4.5 (2.1) to 18 (3.3) pmol/liter after 1 yr of treatment. Body weight decreased from 83.7 (16.4) to 79.4 (16.0) kg (P = 0.002) due to change in the lean mass subcompartment only (P = 0.001) because fat and bone mass was virtually unchanged. Significant increase was observed in REE and in physical activity measured with questionnaires but not measured as daily steps. No significant changes were observed in the control group.

Conclusion: L-T_4 therapy of hypothyroidism associated with significant decrease in body weight and increase in REE. Physical activity measured with questionnaires increased significantly, but not number of daily steps. Despite changes in REE and body weight, fat mass was unchanged during the study. We propose that total body energy equilibrium is maintained during treatment of hypothyroidism and that weight loss observed during such treatment is caused by excretion of excess body water associated with untreated myxoedema. **(*J Clin Endocrinol Metab* 96: E99–E103, 2011)**

Changes in body weight are common in patients with hypothyroidism (1). In general, weight changes are due to either a mismatch between energy intake and energy expenditure leading to accumulation or loss of body fat or a change in body water content secondary to disease or medication. The total daily energy expenditure is a sum of the basal metabolic rate (on the order of 60%), the energy required for physical activity (on average 10–30%), and the thermogenic effect of food (usually 10%) (2).

The thyroid hormones are important determinants of the basal metabolic rate (3), which is a likely cause for the correlation between biochemical thyroid function and

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Abbreviations: fT_4, Free T_4; REE, resting energy expenditure; SF-36, Short Form 36.

body mass index that has been observed even in euthyroid subjects (4). Another possible weight-increasing mechanism in hypothyroidism is a decreasing level of spontaneous physical activity level. In man, hypothyroidism has been shown to influence skeletal muscle metabolism and function (5, 6), and psychomotor slowing and impaired cardiac output has also been shown (7, 8). It may thus be speculated that hypothyroidism is associated with a reduced physical activity level that may contribute some of the body weight changes often observed in this disease.

Finally, hypothyroidism is associated with accumulation of water-binding glycosaminoglycans which led to the term myxoedema (9). It is conceivable that changes in body water content might be involved in the weight changes in hypothyroidism.

To clarify mechanisms involved in body weight changes associated with hypothyroidism, we assessed the body composition, resting energy expenditure (REE) and physical activity level in patients with overt hypothyroidism before and after 12 months of L-T_4 replacement therapy.

Patients and Methods

We consecutively included patients with newly diagnosed autoimmune overt hypothyroidism referred to our unit by their general practitioner. Exclusion criteria were previous thyroid disease, hypothyroidism treated for more than 1 wk, use of medication that could interfere with thyroid function tests, a psychiatric diagnosis, physical incapacity, pregnancy within 12 months or age under 18 or above 80 yr.

Twelve patients were included and underwent physical investigation, measurement of body composition, REE, and evaluation of physical activity. During the study, the patients' general practitioner regularly monitored thyroid function and adjusted the L-T_4 treatment accordingly. Blood samples for the study were obtained at baseline and after 1 yr of L-T_4 treatment. The patients were also investigated after 1, 2, 3, and 6 months with pedometers and the physical activity questionnaire. The patients attended the investigational sessions after an overnight fast.

Informed consent was signed before entering the study, which was approved by the Regional Ethics Committee for North-Jutland and Viborg County, Denmark.

Body composition

Dual-energy x-ray analysis scan (XR-36 wbl; Norland, Fort Atkinson, WI), weighing (SECA, Hamburg, Germany), and height measurements (Harpenden Stadiometer, Crosswell, UK) were performed with participants in light clothing, without shoes, and after voiding.

Resting energy expenditure

REE was measured with indirect calorimetry on an open-circuit system using a Deltatrack II metabolic monitor (Datex, Helsinki, Finland). Flow and gas concentration measurements were performed every minute for 30 min, and the last 20 recordings were used for calculation of REE, expressed as kilocalories per 24 h.

Physical activity

Physical activity was studied using three different methods: step counting and two different questionnaires.

Sealed pedometers (SW-200; Yamax, Tokyo, Japan) worn on the waistband were used for step counting. The patients were asked to ambulate as usual and to wear the pedometer during all waking hours. Measurements were performed on days of ordinary life, not weekends or holidays (10). Measurements with daily step counts fewer than 1000 were considered measurement failures and discarded. The mean of 3 d of pedometer measurements was used for the calculations.

In the physical activity questionnaire, the participants reports how many hours per day they are engaged in nine different levels of physical activity (11). This yields a total physical activity score reflecting physical activity level during an average working day the previous month.

The physical component summary from the general quality-of-life questionnaire Short Form 36 (SF-36) version 1 in Danish was used (12). In both questionnaires, a higher score is better.

Evaluation of constancy of the measurements

A control group was included concurrently to validate the constancy of the measurement methods. Ten patients treated with radioactive iodine for euthyroid goiter more than 1 yr previously was included. All participants were euthyroid throughout the study, two harbored thyroid peroxidase autoantibodies, and none received L-T_4 treatment or antithyroid drugs at any point in time. Apart from a minimal increase in TSH, no significant changes were observed in any of the variables listed in Table 1 in the control patients after 1 yr.

Hormone assays

Serum TSH, free T_4 (fT_4), and free T_3 (fT_3) were measured in duplicate in random order using an electrochemiluminescence immunoassay method on a Modular Analytics E170 (Roche, Germany).

Statistical evaluation

Conformation to normal distribution was tested with quintile-quintile normal distribution plots and the Shapiro-Wilks test. Except for fT_4 hormone levels, where nonparametric tests were used, data followed the normal distribution, and parametric tests were used. A P value <0.05 was considered statistically significant. The Statistical Package for Social Sciences version 11.0 (SPSS, Chicago, IL) and Excel 2003 (Microsoft Corp., Redmond, WA) were used for the calculations.

Results

Patients' characteristics and thyroid function tests at inclusion and after 12 months are shown in Table 1. All hypothyroid patients harbored thyroid peroxidase autoantibodies.

TABLE 1. Characteristics, hormone levels, body composition, REE, and physical activity in hypothyroid patients at inclusion and after 1 yr

	Mean (SD)		
	Baseline	After 1 yr	*P*
Age (yr)	55 (12)	56 (12)	NA
Sex (male/female) (n)	6/6	6/6	NA
Working/retired (n)	5/7	5/7	NA
Smokers (n)	3	3	NA
Serum TSH (mU/liter)	102 (85.0)	2.2 (2.1)	0.004
Serum fT_4 (pmol/liter)	4.5 (2.1)	18 (3.3)	<0.001
Serum fT_3 (pmol/liter)	2.3 (1.0)	4.7 (0.67)	<0.001
Weight (kg)	83.7 (16.4)	79.4 (16.0)	0.002
BMI (kg/m^2)	28.5 (4.79)	26.8 (4.27)	0.001
Fat mass (kg)	28.1 (10.0)	27.8 (8.82)	0.70
Lean mass (kg)	52.3 (11.6)	48.5 (12.0)	0.001
Bone mass (kg)	3.0 (0.52)	3.0 (0.52)	0.26
REE (kcal/24 h)	1320 (244.1)	1460 (256.2)	0.023
REE/lean mass (kcal/24 h · kg)	0.026 (0.003)	0.031 (0.005)	0.004
Steps/d	6594 (2065)	7399 (3181)	0.55
PA score	41.5 (8.39)	48.2 (12.1)	0.025
PCS score	43.9 (9.29)	48.8 (8.65)	0.034

For working status, working means employed and retired means unemployed or retired. REE was measured with indirect calorimetry. Body mass index (BMI) is body weight divided by height squared. Physical activity (PA) score was evaluated by questionnaire (11). The physical component summary (PCS) is from the SF-36 questionnaire (12). *P* values are for differences between baseline values *vs.* after 1 yr. A paired *t* test was used for all variables except fT4 (Wilcoxon test). NA, Not applicable.

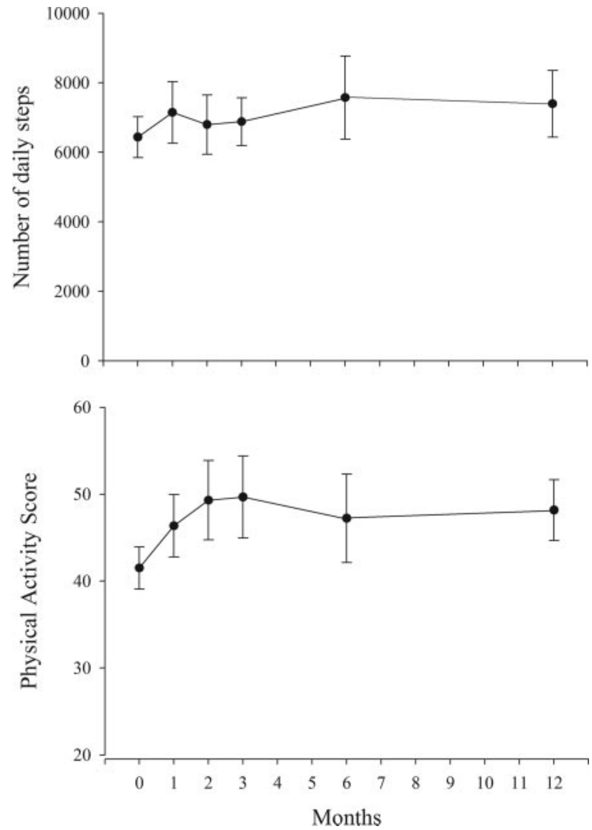

FIG. 1. Mean (±SEM) of the measured number of steps per day (*upper panel*, Friedman $P = 0.41$) and physical activity score (*lower panel*, Friedman $P = 0.018$) at baseline and during 12 months of L-T_4 replacement therapy.

Body composition and REE

Body weight decreased on average 4.3 kg after 1 yr of L-T_4 therapy. This decrease in total body weight was caused by a significant decrease of 3.8 kg in the lean mass subcompartment (Table 1). A small and insignificant decrease was observed in the fat mass subcompartment, and bone mass was equal between the two measurements. At study entry, the patients were asked about their weight 6 months earlier. This recalled weight was 82.1 (14.4) kg, with an estimated increase in weight during the 6 months before inclusion of 2.8 kg. Recalled weight was significantly different from the weight at inclusion ($P = 0.03$) but not after 12 months ($P = 0.37$).

Unadjusted REE as well as REE/lean mass (in kilograms) increased significantly, 11.6 and 21.8%, respectively, after 1 yr of treatment (Table 1).

fT_4 predicted body weight changes during L-T_4 treatment, because baseline fT_4 hormone levels correlated (Spearmans $\rho = 0.64$; $P = 0.035$) to the decrease in body weight during the year. This correlation was also significant for changes in the lean mass subcompartment (Spearmans $\rho = 0.66$; $P = 0.029$) but not for fat (Spearmans $\rho = 0.055$; $P = 0.87$) or bone mass (Spearmans $\rho = -0.30$; $P = 0.37$) changes during the year.

Physical activity level

The step counts varied widely from day to day in all the participants. No significant trend (Friedman, $P = 0.99$) or change ($P = 0.55$) occurred in number of daily steps during the year (Fig. 1, *upper panel*).

The physical activity score during the study (Fig. 1, *lower panel*) increased during the year (Friedman, $P = 0.018$) and after 1 yr ($P = 0.025$). The physical component summary evaluated by the SF-36 increased markedly after 1 yr (Table 1).

Discussion

Changes in body weight during treatment of hypothyroidism

As expected, therapy of hypothyroidism was followed by a moderate decrease in body weight. Intuitively, it might be speculated that such weight loss was mainly caused by loss of body weight due to an increase in energy expenditure. The average increase in REE after 1 yr of therapy was 215 kcal/24 h. If this increase in REE was effective during 6 months of the treatment period, this transforms to combustion of 4.4 kg of fat tissue. This theoretical estimate contrasts the virtual absence of change in body fat observed. We did not quantify the energy intake during the study, but it may be hypothesized that increased energy intake had efficiently counteracted the energy loss from an increase in REE and spontaneous physical activity level in the hypothyroid patients studied. In rats, low doses of T_3 has orexigenic effects without interfering the REE or the locomotor activity (13).

Changes in physical activity during treatment of hypothyroidism

The spontaneous physical activity level has not previously been studied in patients with hypothyroidism. We found that during treatment, physical activity increased as evaluated with questionnaires, but not as daily steps taken. The coefficient of variation during the year was 27% in the physical activity questionnaire compared with 42% for the pedometer measurements. The large variation in the pedometer measurements is a major drawback to detect changes. In keeping with this, we found no significant changes in step count during the year.

Another possible explanation for the lack of difference in step counts is that the measured numbers of steps represent a necessary minimum to maintain the everyday lifestyle habits of the individual, and this may be largely unaffected by the fact that the patients were hypothyroid. The questionnaires, on the other hand, may reflect the self-experienced burden of the necessary physical activity and may also be influenced by the difference between what the individual actually does and assumes he or she should be able to do.

Possible mechanisms of weight loss during treatment of hypothyroidism

The only significant predictor of the 5% decrease in body weight during L-T_4 therapy in hypothyroid patients was baseline fT_4 level. The weight change was caused by a change in lean body mass, because fat mass was largely unaltered. A dual-energy x-ray analysis scan provide a two-component soft tissue model consisting of fat mass and lean mass subcompartments, the latter comprising water, proteins, glycogen, and minerals not tied to bone (14). Hypothyroid patients have reduced capacity of renal free-water excretion (15), increased antidiuretic hormone level (16), and increased amount in tissues of glycosaminoglycans, which have large water-binding capacity (17). Other water-retaining mechanisms from increased protein extravasation to a decreased lymphatic drainage have also been described (18). The high water content of the skin, observed in severe hypothyroidism, originated the term myxoedema (9). Soon after the description of myxoedema, it was noted that therapy with thyroid hormones was followed by an increase in urine output in such patients (19).

Strengths and limitations

Strengths of this study are the evaluation of the spontaneous level of physical activity using three different methods and the addition of a measurement control group. Limitations are the lack of registration of energy intake and of measurement of the thermogenic effect of food.

Conclusion

One year of L-T_4 treatment of hypothyroidism was associated with decreased body weight attributable to a decrease in lean mass because total fat mass was largely unchanged. REE increased during treatment as did the physical activity level measured with two different questionnaires, but not when measured as daily steps taken. We hypothesize that during L-T_4 replacement therapy of hypothyroidism, the total body energy equilibrium is maintained, and the weight loss often observed during such treatment is predominantly due to loss of excess body water accumulated during the state of myxoedema.

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