Weight loss that occurs during levothyroxine treatment of hypothyroidism is predominantly due to loss of excess body water accumulated during the development of myxedema

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SUMMARY

BACKGROUND

Patients with hypothyroidism generally experience alterations in body weight that are either due to energy intake or expenditure, leading to a loss or accumulation of body fat or a change in body water content resulting from second diseases or medical therapy. The basal metabolic rate is the sum of the total daily energy expenditure that is generally in the range of 60%, which includes the energy required for physical activity (approximately 10 to 30% or more), or from the thermogenic effect of food that includes another 10% or more. As thyroid hormones are major determinants of the basal metabolic rate, it is the likely cause of the correlation between biochemical thyroid function and the body mass index. Still, there is another possibility for the weight increase with hypothyroidism, which is a decreasing level of daily spontaneous activity. The authors of this study suggest that changes in body water content might be involved in the weight changes that occur in hypothyroidism. To evaluate this notion, body composition, resting energy expenditure (REE) and physical activity levels in patients with overt hypothyroidism were studied before and after 12 months of levothyroxine (L-T_4) replacement therapy.

PATIENTS AND METHODS

The Study Subjects

The study subjects were patients with newly diagnosed autoimmune overt hypothyroidism who were referred to the authors' clinic. Excluded from this study were patients with previous thyroid disease, hypothyroidism treated for more than 1 wk, use of medication that might interfere with thyroid function tests, a psychiatric diagnosis, physical incapacity, and pregnancy within 12 months, or age less than 18 or above 80 years.

The 12 patients who comprised the study group had a physical examination, measurement of body composition, REE (resting energy expenditure), and evaluation of physical activity. The patient's general practitioner monitored thyroid function and adjusted the L-T_4 treatment as necessary. Blood samples were obtained at baseline and after 1 year of L-T_4 therapy. The patients were studied after 1,2,3, and 6 months with pedometers and a physical activity questionnaire, and were studied after an overnight fast.

Body Composition

A Dual-energy x-ray analysis was 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 Delatatrack II metabolic monitor (Datex, Helsinki, Finland). Flow and gas concentration measurements were performed at every minute for 30 minutes and the last 20 recordings were used for the calculation of REE, expressed as kilocalories per 24 hours.

Physical Activity

Step counting and two different questionnaires were the three methods used to study physical activity. Step-counting was performed with sealed waistband pedometers. The patients were asked to ambulate as usual and to wear the pedometer during all waking hours, which was thus performed during all waking hours in the day, except for weekends and holidays. Fewer than 1000 step counts were considered as measurement failures and were accordingly discarded. A mean of 3 days of pedometer measurements were used for the calculations.

Physical activity was also measured in the physical activity questionnaire, which recorded the number of hours per day during which study participants were engaged in nine different levels of physical activity. This yielded a total physical activity score that reflected physical activity during an average working day during the previous month.

The physical component summary from the general quality-of-life questionnaire Short Form 36 (SF36) version 1 in Danish was used for this study. A higher score is better in both questionnaires.

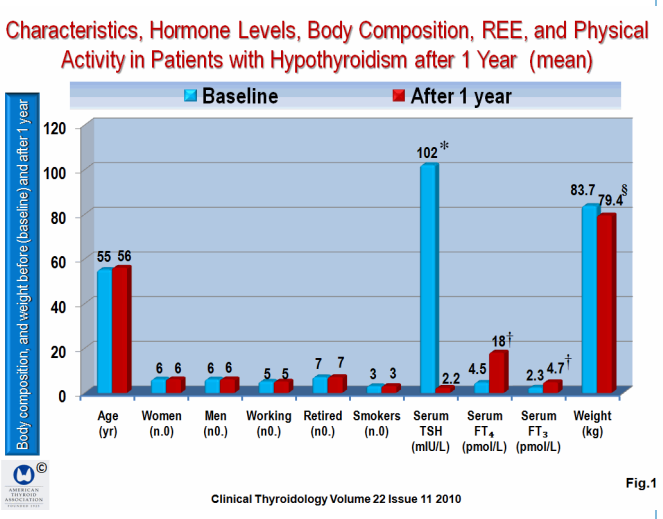

Figure 1. This figure shows the characteristics, hormone levels, body composition, and weight before (baseline) and after 1 year REE = Resting Energy Expenditure. *P=0.004 for serum TSH. Here and elsewhere the comparisons are baseline vs. after 1 year. *P= 0.004; †P< 0.001, for serum FT_4, and FT_3, and §P = 0.002 for weight. The data for this figure and figures 2 and 3 are derived from Table 1 of Karmisholtet.al.

Evaluation of the Consistency of Measurements

A control group was included to validate the consistency of the measurement methods. Also included were 10 patients treated with radioactive iodine for euthyroid goiter more than 1 year previously. All participants were euthyroid throughout the study, although two had thyroid peroxidase autoantibodies, and none received L-T_4 therapy or antithyroid drugs at any time. Except for a minimal increase in TSH, no significant changes were observed in any of the variables in the control patients after 1 year.

RESULTS

Body Composition and REE (Figures 1 and 2)

The characteristics of the study patients and thyroid function tests and after 12 months are shown in Figure 1. Body weight decreased an average of 4.3 kg after 1 year of L-T_4 therapy, which was caused by a significant decrease of 3.8 kg in lean body mass sub compartment *(Figure 2)*. An insignificantly small decrease was observed in the fat mass sub compartment, and bone mass was equal between the two measurements. *(Figure 2)*

On entry of the study, patients were asked about their weight 6 months earlier. This recalled weight was 82.1 kg, with an estimated increase in weight during the 6 months before inclusion of 2.8 kg. This was significantly different from the weight at inclusion (P = 0.03) but not after 12 months (P = 0.37).

After 1 year of treatment, unadjusted REE and REE/lean mass increased significantly to 11.6 and 21.8%, respectively. *(Figure 1)* FT_4 predicted body weight changes during L-T_4 therapy, because baseline FT_4 hormone levels correlated to the decrease in body weight during the year (Spearmans p = 0.64; P = 0.035). This correlation was also significant for changes in lean mass sub compartment (Spearmans P = 0.66; P = 0.029) but not for fat or bone mass changes during the year. *(Figure 2)*

Physical Activity Level

The step counts varied widely from day to day in all of the participants. No significant trend (P = 0.99) or change occurred in the number of daily steps during the year, (P = 0.55). The physical activity score (PAS) increased during the year (Friedman, P = 0.018) and after 1 year (P = 0.025). Also, after 1 year, the physical component summary (PCS score) evaluated by the SF-36 was increased. *(Figure 3)*

CONCLUSION

Body weight decreased on average 4.3 kg after 1 yr of L-T_4 therapy, which was caused by a significant decrease of 3.8 kg in the lean mass sub-compartment

Therapy of hypothyroidism was followed by a moderate decrease in body weight. Although the loss in body weight might have been caused by an increase in energy expenditure, the average increase in REE after 1 year of therapy was 215kcal/24 h. If the 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 is in contrast with the virtual absence of change in the observed body fat.

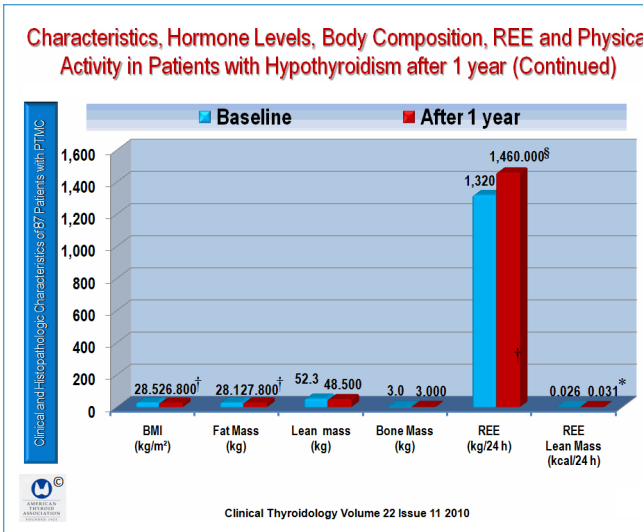

Figure 2. This is a continuation of Figure 1. The figure shows the BMI, fat mass, lean mass and bone mass, REE (kg/24 h) and REE Lean Mass (kcal/24 h). †P <0.001 for BMI; §P0.023 for REE; *P<0.004 for lean mass.

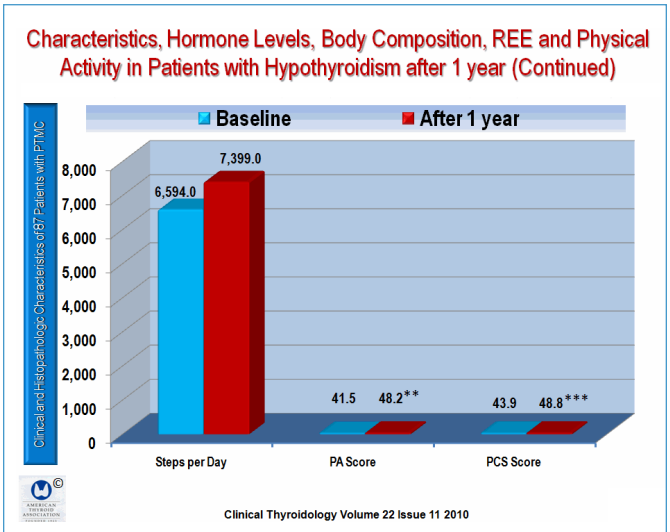

Figure 3. This figure shows the physical activity in patients with hypothyroidism before and after 1 year of L-T_4 therapy. PA score-=physical activity score, **P<0.025; for REE kcal/24 h; *P<0.004 for PCS score.PCS score = physical component summary, which is from SF-36 questionnaire. **P= 0.55 for steps/day;

COMMENTARY

Changes in Physical Activity during Treatment of Hypothyroidism

During treatment, physical activity increased as evaluated with questionnaires, but not as evaluation of daily steps. The coefficient of variation during the year was 27% in the physical activity questionnaire, as compared with 42% for the pedometer measurements. The large variation in the pedometer measurements is a shortcoming, which was reflected by the fact that no significant changes in the step count were observed during the year. The authors suggest that the difference in step counts may have been caused by the everyday life-style habits of individuals, or may be largely unaffected by the fact that the patients had hypothyroidism.

Possible Mechanisms 0f Weight Loss during Treatment of Hypothyroidism

The only significant predictor of the 5% decrease in body weight during L-T_4 therapy was the baseline FT_4 level. The authors suggest that weight change was caused by an alteration in lean body mass, as fat mass was largely unaltered. As hypothyroid patients have reduced capacity of free-water excretion(1), the authors suggested that increased antidiuretic hormone level, and increased amounts of tissue glycosaminoglycans, which have a large water-binding capacity, account for the edema (2). The high water content of the skin, observed in severe hypothyroidism was originated from the term myxedema, shortly after which it was noted that an increased urine output occurred shortly after the administration of thyroid hormone therapy.

Regained weight was significantly different from the weight found at inclusion (P= 0.03) but not after 12 months of therapy. (P = 0.37). One year after L-T_4 therapy of hypothyroidism is associated with decreased body weight attributable to decrease in lean body mass because total fat mass was largely unchanged.

Unadjusted resting energy expenditure (REE) as well as REE lean body mass increased significantly, 11.6 and 21.8% kg respectively, after 1 year of L-T_4 therapy *(Figures 1 and 2)*. FT_4 predicted body weight changes during L-T_4 therapy, mainly because the FT_4 levels were correlated to the decrease in body weight over the year of L-T_4 therapy. This was also correlated to lean body mass sub compartment but not to bone mass.

The authors suggest that the strength of their study is the spontaneous level of physical activity using three different methods and the addition of a measurement control group. On the other hand, they suggest that the limitations of the study are the lack of registration of energy intake and of measurement of the thermogenic effect of food.

Nonetheless, this is an innovative study that provides insight into the mechanisms involved in body weight changes associated with hypothyroidism.

— Ernest L. Mazzaferri, MD, MACP

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