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Caloric Restriction But Not Exercise-Induced Reductions in Fat Mass Decrease Plasma Triiodothyronine Concentrations: A Randomized Controlled Trial

Edward P. Weiss,1,3 Dennis T. Villareal,1 Susan B. Racette,1 Karen Steger-May,2 Bhartur N. Premachandra,4 Samuel Klein,1 and Luigi Fontana1,5

Abstract

Caloric restriction (CR) decreases circulating triiodothyronine (T3) concentration. However, it is not known if this effect is due to body fat mass reductions or due to CR, per se. The purpose of this study was to test the hypothesis that plasma T3 concentration decreases with CR-induced reductions in fat mass but not in response to similar decreases in fat mass that are induced by exercise. Sedentary, nonobese 50- to 60-year-old men and women with no clinical evidence of cardiovascular or metabolic disease and not taking thyroid medications were randomly assigned to 12 months of caloric restriction (n = 18) or exercise-induced weight loss (n = 17) or to a control group (n = 9). Body weight and composition and plasma concentrations of the thyroid hormones T3, thyrotropin (TSH), thyroxine (T4), and free thyroxine (FT4) were measured at baseline and 12 months. Fat mass changed significantly in the CR (−6.3 ± 1.0 kg) and exercise (−5.5 ± 1.0 kg) groups but not in the control group (−0.6 ± 1.4 kg). The changes were not significantly different between the CR and exercise groups. Plasma T3 concentration decreased in the CR group (−9.8 ± 2.0 ng/dL, p < 0.0001) but not in the exercise (−3.8 ± 2.1 ng/dL, p = 0.07) or control (−1.3 ± 2.8 ng/dL, p = 0.65) groups. TSH, T4, and FT4 did not change in any of the study groups. Twelve months of CR decreased circulating T3 concentrations in middle-aged adults. This effect does not appear to be attributable to changes in body fat mass because a comparable decrease in T3 concentration was not observed in response to an exercise-induced fat mass reduction.

Introduction

Thyroid hormones are important because they are closely linked to energy metabolism; they help regulate metabolic rate, and may be regulated by energy balance. It is well documented that circulating concentrations of the thyroid hormone, triiodothyronine (T3), decrease in response to body weight and fat mass losses induced by caloric restriction (CR)1–4 and by CR plus endurance exercise training.5–8 Recently, we found that serum T3 concentrations were lower in lean persons practicing long-term CR, than in age-, gender-, and body fat-matched endurance runners eating a high-calorie diet.9 However, the cross-sectional nature of that study makes it impossible to truly determine if CR, but not exercise, has an effect on circulating T3 concentration.

The purpose of the present study was to conduct a randomized controlled trial to assess the hypothesis that body weight and fat mass reductions induced by long-term CR, but not those induced by increasing exercise energy expenditure without changing energy intake, cause a decrease in circulating T3 concentrations in nonobese humans. This study is part of the CALERIE trial (Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy; Clinical Trials.gov identifier: NCT00099138); reports on other outcomes have been published previously.10–13

Subjects and Methods

Participants

Sedentary, nonsmoking, 50- to 60-year-old men and postmenopausal women with body mass index (BMI) values of

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3Department of Nutrition and Dietetics, Saint Louis University, St. Louis, Missouri.
4Thyroid Specialty Laboratory, St. Louis, Missouri.
5Division of Food Science, Human Nutrition and Health, Istituto Superiore di Sanità, Rome, Italy.
23.5–29.9 kg/m² were recruited for the study. Medical history and physical examination were used to identify and exclude volunteers with cardiovascular disease, diabetes, lung disease, uncontrolled hypertension, and evidence of malignancy. Informed written consent was obtained from all participants and the study was approved by the Human Studies Committee at Washington University School of Medicine. A total of 48 participants started the study interventions, with sample sizes of 19, 19, and 10 for the CR, exercise (EX), and healthy lifestyle control (HL) groups, respectively. Data from 1 CR group participant and 1 EX group participant were excluded because the subjects dropped out and were not available for final testing. Data from two other participants (one each from the EX and HL groups) were excluded because the participants were on thyroid medications. Therefore, the statistical analyses for the present report included 18 subjects in the CR group, 17 in the EX group, and 9 in the HL group.

Interventions

Eligible participants were randomly assigned to CR, EX, or HL group in a 2:2:1 ratio. Individualized diet and exercise prescriptions for the CR and EX groups, respectively, were calculated from baseline total energy expenditure which was determined by the doubly labeled water method as described previously. The CR and EX interventions were designed to result in the same energy deficit. The goal of the CR intervention was to decrease energy intake by 16% from baseline during the first 3 months and by 20% from baseline during the remaining 9 months. To achieve a decrease in energy intake, participants were encouraged to substitute foods with low energy density for those with high energy density and to reduce portion sizes.

Participants randomized to the exercise intervention were instructed to maintain energy intake at baseline levels and to exercise in order to increase total energy expenditure by 16% for the first 3 months and by 20% for the subsequent 9 months. Participants were given exercise energy expenditure prescriptions on a weekly basis and exercised in our facility or on their own. Adherence to the energy expenditure goals was assessed by using heart rate monitors that estimate exercise energy expenditure (S610, Polar Electro Oy, Kempele, Finland). The most commonly used exercise modes were jogging, walking, elliptical machine exercise, cycling, and/or rowing on an ergometer.

Participants in the HL group were offered advice about consuming a healthful diet and were given free access to community-based yoga classes. Participation in dietary consultations and yoga classes was rare. Additional details about the interventions and adherence to the interventions have been presented previously.

Body weight and fat mass

Body weight was measured in the morning, after the participants fasted overnight and while they were wearing only a hospital gown and underwear. Fat mass was measured by dual energy x-ray absorptiometry.

Carbohydrate intake

Carbohydrate intake was measured by using 7-day food diaries and computerized nutrition analysis (Nutrition Data System for Research, versions, 4.05, 4.06, and 5.0, Nutrition Coordination Center, University of Minnesota, Minneapolis, MN). Carbohydrate consumption and several other macronutrient and micronutrient intakes have been reported previously. Carbohydrate intake was included in the present report to help in the interpretation of the results, as carbohydrate deprivation may affect circulating thyroid hormone concentrations.

Thyroid hormones

Venous blood from a forearm or antecubital vein was collected into tubes containing sodium ethylenediaminetetraacetic acid (EDTA). Within 2 hours, plasma was isolated by centrifugation at 4°C and 1000g for 20 minutes and stored at ≤ −20°C. All samples were acquired between 7:00 AM and 11:00 AM; fasting was not required. For 48 hours or more prior to the blood draw, the participants were advised refrain from all exercise or vigorous physical activity. Plasma from venous blood was analyzed for thyroxine (T4) concentration by fluorescence polarization immunoassay and for concentrations of T3, thyrotropin (TSH), and free thyroxine (FT3) by microparticle enzyme immunoassay (Abbott Laboratories, North Chicago, IL).

Statistical analyses

Analysis of covariance (ANCOVA) was used to compare baseline to 12-month changes in outcome variables among study groups with adjustment for baseline values. Tukey’s tests were used for paired comparisons of mean changes. Within-group changes were assessed using the least squares means from the ANCOVA. Analyses were performed using SAS software for Linux (version 9.1.3, SAS Institute Inc., Cary, NC). Statistical tests were two-tailed, and significance was accepted at p ≤ 0.05.

Results

Participants

The relative distribution of men and women participants was similar across groups; CR (39% men), EX (35% men), and HL (44% men). At baseline, the mean (± standard deviation [SD]) age was 55 ± 3, 59 ± 3, and 55 ± 2 years and body mass index (BMI) was 27.1 ± 2.5, 27.0 ± 1.9, and 28.0 ± 1.4 kg/m² in the CR, EX, and HL groups, respectively.

Body weight and fat mass

Body weight and fat mass data for a slightly larger sample have been previously presented in detail and are presented here to assist in the interpretation of the thyroid hormone data. Body weight and fat mass decreased significantly in the CR and EX groups but not in the HL group (Table 1). The weight and fat mass changes were not different between the CR and EX groups.

Carbohydrate intake

Total daily carbohydrate intake decreased in the CR group but not in the EX or HL groups; the change in the CR group was significantly different from that in the EX group (Table 1). In contrast, dietary carbohydrate as a percentage of energy intake remained unchanged in all groups.
Thyroid hormones

Plasma T₃ concentration decreased in the CR group but not in the EX or HL groups; the change in the CR group was significantly different from that in the HL group (Table 2). Plasma concentrations of TSH, T₄, and FT₄ did not change in any group (Table 2).

Discussion

The results from the present study demonstrate that CR-induced reductions in body weight and fat mass cause a significant decrease in circulating T₃ concentration while similar reductions in body weight and fat mass induced by exercise have little or no effect on plasma T₃ concentration. These findings have important implications because T₃ might mediate the effect of CR on oxidative stress and longevity.⁴,¹⁵ However, from a weight loss and weight maintenance perspective, they also suggest that CR-induced weight loss may be more difficult to maintain than weight loss induced by exercise because low T₃ in euthyroid individuals is predictive of long-term weight gain,¹⁶ possibly because of its effect on metabolic rate. Although on average, T₃ concentrations remained in the normal range, the 11% (9.8 ng/dL) decrease in the CR group would be expected to result in a 14 kcal/d decrease in resting metabolic rate (independent of changes in lean mass) based on published equations.¹⁷ To put the magnitude of this metabolic alteration in perspective, a positive energy balance of 14 kcal/d would result in an annual weight gain of 0.7 kg, which is comparable to the typical 0.3–1.0 kg/yr adulthood weight gain in the United States.¹⁸,¹⁹

Table 1. Body Weight, Fat Mass, and Carbohydrate Intake

<table>
<thead>
<tr>
<th></th>
<th>CR (n = 18)</th>
<th>EX (n = 17)</th>
<th>HL (n = 9)</th>
<th>Among group p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)ᵃ</td>
<td>78.9 ± 2.2</td>
<td>76.9 ± 2.6</td>
<td>82.9 ± 3.9</td>
<td>0.004</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change</td>
<td>−8.3 ± 1.1ᵇ,c</td>
<td>−6.8 ± 1.2ᵇ,c</td>
<td>−1.3 ± 1.6</td>
<td></td>
</tr>
<tr>
<td>Fat mass (kg)ᵇ</td>
<td>26.4 ± 1.3</td>
<td>25.6 ± 1.4</td>
<td>26.7 ± 1.2</td>
<td>0.004</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change</td>
<td>−6.3 ± 1.0ᵇ,c</td>
<td>−5.5 ± 1.0ᵇ,c</td>
<td>−0.6 ± 1.4</td>
<td></td>
</tr>
<tr>
<td>Carbohydrate intake (g/d)</td>
<td>Baseline</td>
<td>243 ± 22</td>
<td>237 ± 12</td>
<td>289 ± 22</td>
</tr>
<tr>
<td>Change</td>
<td>−29 ± 10ᵇ,d</td>
<td>11 ± 10</td>
<td>−6 ± 15</td>
<td></td>
</tr>
<tr>
<td>Carbohydrate intake (% energy intake)</td>
<td>Baseline</td>
<td>46.7 ± 2.7</td>
<td>46.2 ± 1.5</td>
<td>52.1 ± 2.7</td>
</tr>
<tr>
<td>Change</td>
<td>2.0 ± 1.3</td>
<td>0.4 ± 1.4</td>
<td>−2.1 ± 2.0</td>
<td></td>
</tr>
</tbody>
</table>

ᵃBody weight and fat mass data have been presented previously for a slightly larger sample¹³ and are presented here to assist in the interpretation of the thyroid hormone data.

ᵇBaseline data are arithmetic means ± SE; change data are least squares means ± SE after adjustment for baseline values.

ᶜ⁺p ≤ 0.05 within group using adjusted change from ANCOVA.

ᵈ⁺p ≤ 0.05 versus HL group.

 Thyroid hormones

Plasma T₃ concentration decreased in the CR group but not in the EX or HL groups; the change in the CR group was significantly different from that in the HL group (Table 2). Plasma concentrations of TSH, T₄, and FT₄ did not change in any group (Table 2).

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Table 2. Plasma Concentrations of Thyroid Hormones

<table>
<thead>
<tr>
<th></th>
<th>CR (n = 18)</th>
<th>EX (n = 17)</th>
<th>HL (n = 9)</th>
<th>Among group p</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH, µIU/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.01 ± 0.10</td>
<td>1.31 ± 0.17</td>
<td>1.11 ± 0.19</td>
<td>0.77</td>
</tr>
<tr>
<td>Change</td>
<td>0.12 ± 0.1</td>
<td>0.11 ± 0.1</td>
<td>−0.01 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>T₃, ng/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>88.9 ± 2.4</td>
<td>95.9 ± 3.3</td>
<td>92.6 ± 3.9</td>
<td>0.03</td>
</tr>
<tr>
<td>Change</td>
<td>−9.8 ± 2.0ᵇ</td>
<td>−3.8 ± 2.1</td>
<td>−1.3 ± 2.8</td>
<td></td>
</tr>
<tr>
<td>T₄, µg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>6.29 ± 0.23</td>
<td>6.66 ± 0.35</td>
<td>6.56 ± 0.32</td>
<td>0.10</td>
</tr>
<tr>
<td>Change</td>
<td>−0.09 ± 0.2</td>
<td>−0.35 ± 0.2</td>
<td>0.32 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>FT₄, ng/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.08 ± 0.05</td>
<td>0.98 ± 0.03</td>
<td>0.92 ± 0.05</td>
<td>0.93</td>
</tr>
<tr>
<td>Change</td>
<td>−0.01 ± 0.04</td>
<td>−0.03 ± 0.04</td>
<td>−0.04 ± 0.06</td>
<td></td>
</tr>
</tbody>
</table>

ᵃ⁺p ≤ 0.05 within group using adjusted change from ANCOVA.

ᵇ⁺p ≤ 0.05 versus HL group.

 Baseline data are arithmetic means ± SE; change data are least squares means ± SE after adjustment for baseline values.

 TSH, thyroid stimulating hormone; T₃, triiodothyronine; T₄, thyroxine; FT₄, free thyroxine; CR, caloric restriction; EX, exercise; HL, healthy lifestyle.
The year-long energy deficits induced by the CR and exercise interventions were similar, as evidenced by similar changes in fat mass (Table 1). Furthermore, the decrease in serum leptin concentration, as reported previously, was not different between the CR (−61%) and exercise groups (−62%), suggesting that metabolically, the energy deficits were sensed as similar by the adipose tissue. These results suggest that the decrease in plasma T3 concentration that has been previously associated with reductions in body weight and fat mass is induced by a reduction in energy intake and not due to negative energy balance itself.

Furthermore, because body weight was stable during the last 3 weeks of the study (3 week changes: CR, +0.1 kg; EX, −0.6 kg as reported in Weiss et al.), these changes can not be attributed to a negative energy balance at the time of follow-up testing.

The thyroid gland secretes small amounts of T3. However, most circulating T3 is produced by deiodination of T4 in the liver and other tissues. Because TSH, T4, and FT4 were not altered by CR, our results are consistent with the notion that T3 concentrations decreased as a result of lower peripheral conversion of T4 to T3 instead of a decrease in secretion from the thyroid gland. While the precise mechanism involved in reduced peripheral conversion of T3 to T4 in the CR group is not apparent, it is possible that the reduction in ATP and/or cofactors in the CR group may have partially inhibited the type 1 T4 deiodinase activity, resulting in decreased circulating T3 levels.

Low circulating T3 concentrations can also be caused by hypothyroidism. However, CR did not cause clinical or subclinical hypothyroidism in our participants because TSH did not increase, despite the reduction in circulating T3 concentrations. In addition, low T3 concentrations are associated with elevated systemic inflammation in a condition known as “sick euthyroid syndrome.” However, our subjects did not have evidence of systemic inflammation and CR is known to decrease markers of systemic inflammation.

A limitation of the present study is that we did not measure free T3 or thyroxine-binding globulin (TBG) concentrations and fat mass is induced by a reduction in energy intake and not due to negative energy balance itself.

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A limitation of the present study is that we did not measure free T3 or thyroxine-binding globulin (TBG) concentrations and therefore do not know if the biologically active fraction of circulating T3 was affected by CR. However, previous human studies suggest that total T3 and free T3 decrease together in response to CR. In response to unintentional CR during the Biosphere 2 experiment, total and free T3 concentrations both decreased while TBG concentrations remained unchanged. Additionally, both total and free T3 concentrations are lower in long-term practitioners of CR, as compared to age-matched lean endurance athletes and sedentary controls. Therefore, it seems reasonable to expect that the reductions in total T3 concentration seen in the present study were accompanied by decreases in free T3 concentrations.

We specifically studied 50- to 60-year-old men and women because one of the objectives of the larger CALERIE trial was to determine if CR reverses the biologic effects of aging (younger subjects would not have any aging effects to reverse). Although our study results may not be directly generalizable to younger individuals, previous studies have shown that CR decreases total T3 concentrations in men and women aged 26–50 years, albeit with shorter interventions. Furthermore, CR has been shown to lower T3 concentrations in both young (approximately 13 years) and old (approximately 26 years) rhesus monkeys (median and maximal lifespan of approximately 25 and 40 years, respectively) and the effect may be somewhat greater in younger monkeys. Taken together, the findings from these previous studies suggest that our results are likely applicable to younger men and women than we studied, although it is also possible that larger T3 reductions occur in young adults. In summary, a CR-induced fat mass reduction caused a significant decrease in plasma T3 concentration. In contrast, a similar change in fat mass induced by exercise had little or no effect on T3, although the exercise effect may have been nonsignificant because of the small sample size and limited statistical power. Studies on rodents have demonstrated that CR decreases circulating T3 concentrations, body temperature, resting oxygen consumption, and oxygen free-radical-induced tissue damage, and slows aging. The present results add to the accumulating body of evidence that humans undergo some of the same adaptations to CR as do rats and mice.

Acknowledgments

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References


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