Clinical and Laboratory Report

Thyroid Function and Energy Intake During Weight Gain Following Treatment of Hyperthyroidism

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Objective: Individuals with hyperthyroidism lose weight despite increased appetite and food intake, and weight is regained after treatment of hyperthyroidism. We asked whether this weight regain is purely a function of lowered metabolic rate coincident with lowered thyroid hormone concentrations or if the weight gain is related to food-energy overconsumption.

Methods: Ten unselected patients with hyperthyroidism treated with ^{131}I were studied. The following measurements were made at 0, 1, 2, 3, 6, and 12 months: total food energy, carbohydrate, fat and protein consumption; serum thyroxine (T_4); serum triiodothyronine (T_3); T_3 resin uptake; serum thyroid stimulating hormone (TSH); weight; height; and 24-hour urinary urea excretion.

Results: Inverse changes in body weight and food energy consumption/kg throughout the period of observation was a striking finding (mean initial weight 67.1 ± 5 kg, final weight 76.4 kg ± 3 kg, premorbid weight 77.1 ± 5 kg). The initial and final food energy intake was 3005 ± 199 and 2597 ± 137 Kcal/24 hrs, respectively. The thyroid hormone concentrations declined inversely relative to weight gain during the first months of the study, but later the thyroid hormones increased while weight gain continued. Initial serum T_4 15.0 ± 1 value at three months was 4.0 ± 1.0 mg/dl, final T_4 11.0 ± 1.

Conclusion: We conclude that weight gain following treatment of hyperthyroidism is due to 1) reduction in metabolic rate consequent upon the decreased thyroid hormone concentrations and 2) food energy intake which was initially greater than required to maintain individuals' premorbid weight. As body weight increased, food intake declined and both reached an asymptotic limit.

INTRODUCTION

It is well known that hyperthyroid individuals lose weight despite increased appetite and food intake and that weight is regained with treatment. In a previous study [1], we demonstrated that the weight loss associated with hyperthyroidism is about 15% of the premorbid baseline weight before treatment is instituted and this was independent of the individual's actual premorbid weight. In that study weight gain after treatment of hyperthyroidism occurred primarily within the first three months, and by twelve months the individual's body weight had approached the premorbid weight where it then stabilized. In our previous study, we demonstrated an asymptotic approach to the premorbid mean weight over time, but did not measure food intake.

In the present study, we prospectively examined the total daily food energy intake and relative contributions of dietary carbohydrates, fats and proteins ingested by hyperthyroid patients at the time of initial evaluation and at frequent intervals during the first year after treatment. We then analyzed the patterns of weight gain, food energy and thyroid status. We were particularly interested in whether rapid connection of the hyperthyroidism would result in an increase in food energy intake when the hyperthyroidism was treated, but before body weight had been normalized. To our knowledge the degree of fuel over-consumption in thyrotoxicosis has not been well

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documented in the literature, nor has the food-energy response to treatment of the thyrotoxicosis.

MATERIALS AND METHODS

Subjects

Ten unselected subjects with hyperthyroidism were studied. All were diagnosed, treated and followed at the Veterans Administration Medical Center, Minneapolis, MN. Their mean age was 59 ± 3.8 years (mean ± standard error), range 39 to 71 years. All but one were men. Mean pretreatment weight was 67.1 ± 5.0 kilograms, range 44.5 to 92.1. Diagnosis of hyperthyroidism was based on clinical findings and thyroxine (T_4) values of greater than 12.5 μg/dL, triiodothyronine (T_3) values greater than 202 ng/dL and thyroid stimulating hormone (TSH) values of less than 0.2 μIU/mL. All subjects signed an informed consent and the study was approved by the Medical Center Committee on Human Subjects. The subjects studied were entirely different from those reported previously.

METHODS

Subjects were studied immediately prior to treatment and at the end of months one, two, three, six, and twelve post-treatment. Each time the subjects were admitted to a clinical research center (Special Diagnostic and Treatment Unit) for three days. They were given an unrestricted diet of their own choice. The total food energy intake for each day and the amounts of carbohydrate, fat and protein ingested were calculated by staff nutritionists from the food consumed. Day to day variation in total food-energy intake over the three days of evaluation at each visit were determined and were not significant. For diet analysis three days of measurements were meaned and used for all calculations. During each visit the following also were obtained: serum thyroxine (T_4) (normal range 4.0–12.5 μg/dL); radioimmunoassay kit from Bio-Rad Laboratories, serum triiodothyronine (T_3) (normal range 78–202 ng/dL); radioimmunoassay kit from Bio-Rad Laboratories, T_3 resin uptake (normal range 25–35%); kit from Amersham Co., serum thyroid stimulating hormone (TSH) (normal range 2–6 μIU/L); radioimmunoassay kit from Kallestad Laboratories, and 24-hour urinary urea nitrogen excretion. Urinary urea nitrogen was measured by an enzymatic conductivity rate method using kits purchased from Becklin Labs. Weight and height were recorded on each visit. Premorbid weight is the actual recorded weight prior to the development of thyrotoxicosis in eight patients or was based on the patients' estimated weight loss due to hyperthyroidism in two cases. Baseline weight is that recorded at the time of initial evaluation. All patients received radioactive iodine (^{131}I) treatment at the time of initial hospital admission. Mean ^{131}I dose was 12.7 millicuries ± 3.1, range 4 to 30. Replacement thyroxine was begun at subsequent visits when the patients were clinically hypothyroid or when the serum thyroxine had decreased to less than 4.0 μg/dL. Most commonly this occurred at three months after treatment. Data represent means ± standard errors of the means unless indicated otherwise. Data representing prospective follow-up of these patients with respect to their weight, food-energy intake and thyroid-function studies have been analyzed for change by repeatedly measured ANOVA. Fisher's Least Significant Difference test was used to determine the earliest point of difference from initial values.

RESULTS

Changes in serum T_4 and T_3 values were as expected (Fig. 1). They decreased over the first one to two months after radioiodine treatment and, on average, moved briefly into the hypothyroid range before treatment with thyroid hormone replacement normalized the values. Serum T_4 at initial evaluation was 15 ± 0.9 μg/dL, range 12–20 (Fig. 1). It reached a low value of 4.0 ± 1.0 μg/dL, (range 1 to 12) at three months. After replacement thyroxine therapy, the serum T_4 value was 11 ± 1.0 μg/dL at month twelve. When the serum T_4 level was analyzed by ANOVA with patient and time as independent variables, the F-ratio for patients was 1.94 ($p = 0.070$), indicating little variance between patients. The F-ratio for time in the analysis of T_4 changes was 13.4 ($p < 0.001$), indicating a strong and parallel change in T_4 values over the course of the study. The ANOVA result further indicates that the graph of mean values over time is a reasonable description of a typical expectation. The decline in T_4 compared to starting values became significant by month two. Changes in serum T_3 (Fig. 1) paralleled the serum T_4 values. The ANOVA for T_3 also was similar to that for T_4. The F-ratio for patients was 2.0 ($p = 0.062$), and the F-ratio for time was 12.0 ($p < 0.001$), indicating minimal variance among patients, but strong and parallel changes occurring in the individual patient T_3 values over time. As with serum T_4 the T_3, decrease became statistically significant by month two.

There were marked differences in individual TSH values after treatment because of variation in TSH response to a falling or low serum T_3 and T_4. The TSH was 1.2 ± 0.3 μU/mL, (range 0 to 1.6) before treatment. It increased to 9 ± 8 μU/mL at twelve months. However the range was very wide (0.8 to 47.3 μU/mL), and similarly wide variations were evident at most other time points. Because of several missing data points, a formal analysis by ANOVA was not possible, but given the variance in the data already alluded to, it is unlikely that a consistent, parallel trend over time would be found with TSH.

Mean weight at the time of diagnosis and treatment was 12.6% less than premorbid weight, with a standard deviation of 6%. It then increased in an asymptotic fashion over the ensuing

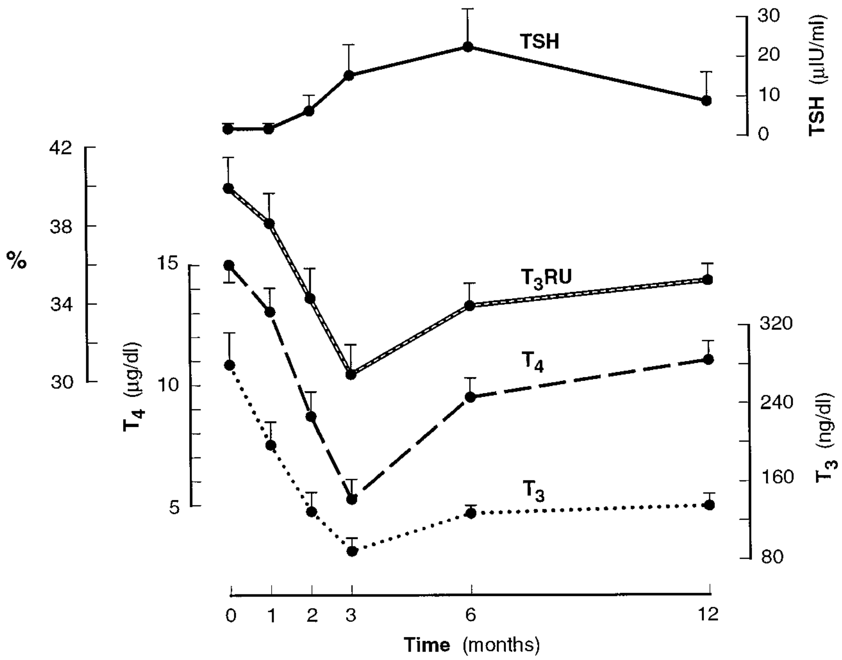

Fig. 1. Changes over the 12 months following ^{131}I treatment of hyperthyroidism in thyroxine (T_4), tri-iodothyronine (T_3), T_3 resin uptake (T_3RU), and thyroid stimulating hormone (TSH).

twelve months until mean body weight was within 1% of the subject's mean premorbid weight (Fig. 2). The large range of patient weights (mean premorbid weight 77.1 ± 5.0 kilograms, range 48.5 to 96.6 kilograms) was reflected in the ANOVA where the F-ratio for patients was 227.5 ($p < 0.001$), but the association of time and weight was robust and parallel, with an F-ratio of 22.5 ($p < 0.001$). Following treatment, a significant increase had occurred within two months. If each weight is expressed as the difference from premorbid weight, the variation among individuals is still significant, though less so (F-ratio 14.9, $p < 0.001$) and the association of time and weight is unchanged.

Food intake declined throughout the observation period and was a mirror image of the pattern seen with body weight (Fig. 2). Mean food-energy intake at initial evaluation was 3005 ± 199 kilocalories/24 hr with a range of 1733 to 3652 kilocalories/24 hours. Food energy intake declined asymptotically throughout the observation period to a mean plateau value of 2597 ± 137 kilocalories/24 hours (range 1858 to 3533). When total intake is assessed by ANOVA, a significant F-ratio is found for the association with patients ($F = 18.6$; $p < 0.001$), but the effect of time, while significant, is not as strong as in the analysis of other variables ($F = 3.2$, $p = 0.016$). If the intrinsic variability in intake associated with body size is adjusted for by expressing the food energy intake as kilocalories/kg, the variance produced by patients is reduced ($F = 8.6$, $p < 0.001$) and

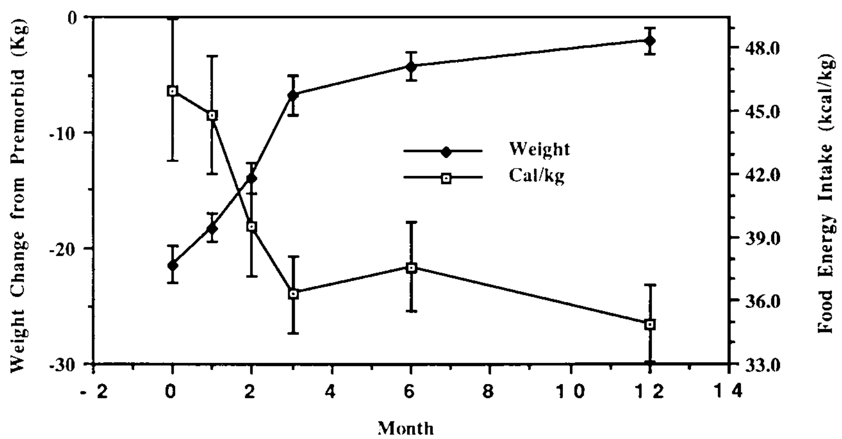

Fig. 2. Changes over the 12 months following ^{131}I treatment of hyperthyroidism in body weight and in food energy intake (adjusted for body weight). The mean premorbid weight of the subjects was 77.1 ± 5 Kg.

the effect of time on kilocalories/kg intake (Fig. 2) is more consistent and parallel ($F = 8.3$, $p < 0.001$). A statistically significant change from starting levels in total fuel intake or kilocalories/kg did not occur until month three. Relative contribution to total food energy of carbohydrate was 46%, fat 36% and protein 18% at every time point from baseline to month twelve. Urinary-urea nitrogen excretion was 500 ± 54 mmol/24 hr at initial evaluation, was 357 ± 18 mmol/24 hr at three months and 321 ± 71 mmol/24 hr at 12 months after treatment.

DISCUSSION

Clearly, weight gain following treatment of thyrotoxicosis is primarily due to reduced concentrations of thyroid hormones and presumably in metabolic rate associated with these hormones. Reduced metabolic rate, though not measured in this study, is implied by consistent weight gain without increased (indeed ultimately decreased) food intake. Two other observations are of note: first, that food intake during hyperthyroidism, while increased relative to levels found one year post-treatment, was evidently not increased enough to prevent weight loss, and second, that one year after hyperthyroidism treatment, body weight had risen to pre-morbid values.

Food energy intake in these subjects while hyperthyroid was substantially greater than required when they had returned to a premorbid body weight. The data are consistent both with clinical experience and with previous studies. Alton and O'Malley [2] have reported, using seven-day dietary recall, that calculated food-energy intake is significantly higher in thyrotoxic patients than normal controls. Following carbimazole therapy it decreased by 37%. The study was terminated when the serum T_4 reached a normal value. At that time the weight gain in the subjects was 10% above their weight prior to the treatment of thyrotoxicosis. Thus, the final weight that may have been reached in these subjects is not known. In the present study in which actual food intake was measured, the decrease was only 22.5% one year after treatment and at a time when the majority of the weight lost had been restored. Alton and O'Malley also speculated that hyperthyroidism could stimulate appetite in a long term and potentially irreversible way, thereby resulting in long-term weight gain. Far from demonstrating persistent stimulation of appetite, our subjects exhibited a consistent decline in appetite as weight was restored to near premorbid values.

Thyroxine administration in supraphysiological doses to healthy rats and mice decreased body weight in spite of an increase in caloric intake [2–4]. Our observations also indicate weight loss in humans despite increased food energy intake. This must be due to an increase in metabolic rate out of proportion to increased food energy ingestion and implies that appetite compensation is incomplete. Previous calculations of food energy necessary to maintain weight stability during human hyperthyroidism are consistent with this observation. Sato et al. [5] have reported that during precise diet administration, more than 60 kilocalories per kilogram per day are required to prevent weight loss in thyrotoxicosis patients. Boothby and Sandiford [6] reported that during careful balance studies, 74 kilocalories per kilogram per day were necessary in order to maintain nitrogen balance in thyrotoxic patients. Our subjects voluntarily consumed only 48 kilocalories per kilogram per day while hyperthyroid and, consequently, were losing weight. The mechanism or mechanisms limiting appetite compensation during hyperthyroidism are not known.

Resumption of premorbid body weight within one year after treatment of hyperthyroidism is an observation made previously by one of us [1]. A striking finding of the present study was the inverse change in body weight and food energy consumption throughout the period of observation. Also noteworthy is that food intake did not increase post hyperthyroidism. This could have facilitated weight gain and might have been expected, since in the hyperthyroid state compensation for the excessive energy production is incomplete. The potential mechanisms responsible for resumption of previous body weight and for guiding the role of appetite in weight gain are incompletely understood, but potential explanations deserve comment.

It is possible that food-energy intake is independently determined by the level of thyroid hormones. If this were the mechanism, we would have expected caloric intake to follow the course of the thyroid hormones during the observation period. This prediction generally held for both thyroxine (T_4) and tri-iodothyronine (T_3) during the first months of observation, when thyroid levels were progressively falling. During the last months, however, the hormone concentrations and food energy intake moved in different directions.

An association of food energy consumption with T_3 concentration is well known [7–9]. However, it has generally been found that food energy determined the T_3 level, not the reverse. Such an association is particularly well described during starvation and refeeding [7,8], but an increase in T_3 with increased food energy intake also is well documented [9].

A second possible explanation is that food energy consumed was determined by the difference in body weight from premorbid body weight, i.e., by the magnitude of a body weight error signal. The pattern of change in weight and food consumption we observed is consistent with this possibility. The observation that, after treatment, weight returns to that present before the development of hyperthyroidism, as well as the remarkable inverse relationship between weight and food-energy intake following treatment is particularly compelling for such a cybernetic system. In this context, it is interesting to note that in a study in which thyroxine was administered to mice, the provoked increase in food energy consumption was delayed almost ten days from the beginning of thyroxine administration and also lagged by three to six days after a measurable increase in metabolic rate [4]. This suggests that it is the thyrotoxicosis-induced deviation from usual body weight that determines the magnitude of caloric intake adjustment; that is, deviation of body weight from a set-point value generates an error signal that produces a proportional change in food-energy intake. One observation made in this study not explained by set-point theory is the incomplete appetite compensation associated with hyperthyroidism. An unknown process associated with hyperthyroidism and not with euthyroidism or hypothyroidism [1] must be invoked.

The issue of the existence of a set point for body weight regulation has been controversial for some time [10,11]. Nonetheless, there is evidence, both in man [12,13] and in animals [14], that set point regulation occurs. In man, the evidence has primarily been related to a predictable recovery of body weight after experimental interventions of starvation [12] and over-nutrition [13]. Our previous study [1] and particularly the present one are particularly informative with respect to understanding the set-point regulation of body weight. In the case of thyrotoxicosis, we have an abnormal, but spontaneously occurring stressor which results in weight loss.

A third possible interpretation of the increase to premorbid weight with declining food energy intake is re-equilibration of weight after restoration of usual food intake and metabolic rate. In this interpretation, body weight is seen to be at a settling point determined by average levels of food energy intake and total energy expenditure. When the hyperthyroidism is treated, the resting component of energy expenditure gradually decreases to premorbid values. We can see the gradual decline in energy intake as a similar phenomenon. Why the appetite decline is gradual instead of abrupt and associated with treatment, cannot be determined from these data. It may be that change in behaviors are generally gradual.

A significant difference in macronutrient composition of food ingested before or after treatment was not observed. There was a proportional decrease in carbohydrate, protein and fat. This contrasts with a previous report suggesting that thyrotoxicosis particularly stimulated a craving for carbohydrates [2].

In summary, we have confirmed that treatment of hyperthyroidism is associated with an asymptotic return to premorbid body weight. Mean measured food-energy intakes were substantially higher during hyperthyroidism relative to values obtained upon return to normal health, and mean intake fell during the observation period. The pattern was inverse to the rise in mean body weight. We conclude that weight gain following treatment of hyperthyroidism is due to a reduction in metabolic rate consequent to the decreased thyroid hormone concentration and not to an increased food-energy intake. As body weight increased, food intake declined and both reached an asymptotic limit. This suggests that body weight deviation from set-point is a major factor controlling fuel intake.

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REFERENCES

1. Hoogwerf BJ and Nuttall FQ: Long-term weight regulation in hyperthyroid and hypothyroid subjects. Am J Med 76:963–970, 1984.
2. Alton S and O'Malley BP: Dietary intake in thyrotoxicosis before and after adequate carbimazole therapy. Clin Endocrinol 23:517–520, 1985.
3. Wang GW: Effect of thyroid feeding on spontaneous activity of albino rat and its relation to accompanying physiologic changes. Bull Johns Hopkins Hosp 40:304–307, 1927.
4. Donhoffer SZ and Vonotzky J: Effect of thyroxine on food intake and selection. Am J Physiol 150:334–339, 1947.
5. Sato T, Saito S, Kokubun M, Saito T, Ito M, Yamamoto M, Kaise K and Kaise N: Carbohydrate metabolism in thyrotoxicosis with special reference to its relation to caloric intake. Tohoku J Exp Med 136:343–348, 1982.
6. Boothby WM and Sandiford I: The total and nitrogenous metabolism in exophthalmic goitre. JAMA 81:795–800, 1923.
7. Portnay GI, O'Brian JT, Bush J, Vagenakis AG, Azizi F, Arky RA, Ingbar S and Braverman LE: The effect of starvation on the concentration of binding of thyroxine and triodothyronine in serum on the response to TRH. J Clin Endocrinol Metab 39:191–194, 1974.
8. Chopra IJ and Smith SR: Circulating thyroid hormones and thyrotrophin in adult patients with protein-calorie malnutrition. J Clin Endocrinol Metab 40:221–227, 1975.
9. Danforth E, Horton ES, O'Connel M, Sims EAH, Burger AG, Ingbar SH, Braverman L and Vagenakis AG: Dietary-induced alterations in thyroid hormone during over-nutrition. J Clin Invest 64:1336–1347, 1979.
10. Garrow J: "Balance and Obesity in Man." London: North Holland Publishing Co., Ltd., 1974.
11. Stunkard AJ: Anorectic agents lower a body weight setpoint. Life Sci 30:2043–2055, 1982.
12. Keys A, Brozek J, Henshel O, Mickleson O and Taylor HL: "The Biology of Human Starvation." Minneapolis/St. Paul: University of Minnesota Press, 1950.
13. Sims EAH and Horton ES: Endocrine and metabolic adaptations to obesity and starvation. Am J Clin Nutr 21:1455, 1968.
14. Keesey RA: Physiological regulation of body weight and the issue of obesity. Med Clin North Am 73:15–28, 1989.

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