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# Plasma concentrations of free triiodothyronine predict weight change in euthyroid persons[2]

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## Abstract

**Background—**Factors that influence energy metabolism and substrate oxidation, such as thyroid hormones (THs), may be important regulators of body weight.

**Objective—**We investigated associations of THs cross-sectionally with obesity, energy expenditure, and substrate oxidation and prospectively with weight change.

**Design—**Euthyroid, nondiabetic, healthy, adult Pima Indians ($n$ = 89; 47 M, 42 F) were studied. Percentage body fat (%BF) was measured by using dual-energy X-ray absorptiometry; sleeping metabolic rate (SMR), respiratory quotient, and substrate oxidation rates were measured in a respiratory chamber. Thyroid-stimulating hormone (TSH), free thyroxine ($T_4$), free triiodothyronine ($T_3$), and leptin concentrations were measured in fasting plasma samples.

**Results—**TSH, but neither free $T_3$ nor free $T_4$, was associated with %BF and leptin concentrations ($r$ = 0.27 and 0.29, respectively; both: $P \leq 0.01$). In multiple regression analyses adjusted for age, sex, fat mass, and fat-free mass, free $T_3$ was a positive predictor of SMR ($P$ = 0.02). After adjustment for age, sex, %BF, and energy balance, free $T_3$ was a negative predictor of 24-h respiratory quotient ($P < 0.05$) and a positive predictor of 24-h lipid oxidation rate ($P$ = 0.006). Prospectively, after an average follow-up of 4 ± 2 y, the mean increase in weight was 3 ± 9 kg. Baseline $T_3$ concentrations were associated with absolute and annual percentage of changes in weight ($r = -0.27$, $P$ = 0.02, and $r = -0.28$, $P$ = 0.009, for the age-and sex-adjusted associations, respectively).

**Conclusions—**In euthyroid Pima Indians, lower free $T_3$ but not free $T_4$ concentrations were an independent predictor of SMR and lipid oxidation and a predictor of weight gain. This finding indicates that control of $T_4$-to-$T_3$ conversion may play a role in body weight regulation.

### Keywords

Thyroid hormones; energy expenditure; lipid oxidation; obesity; respiratory chamber

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## INTRODUCTION

Obesity is a disease of energy imbalance. Lower 24-h energy expenditure (EE) (1), lower resting metabolic rate (1), and higher respiratory quotient (RQ), which indicates a lower whole-body lipid oxidation (LOX) rate (2,3), are all predictors of weight gain. Even after adjustment for the main predictors of these metabolic variables (ie, body composition, body size, fat distribution, age, sex, familiar aggregation, and glucose tolerance status), a significant proportion of the variance in 24-h EE (4,5), resting metabolic rate (6), and sleeping EE (4,5) remains unexplained. This unexplained variance is even larger for RQ (3,5). For the prevention or treatment of obesity or both, therefore, it is important to identify additional physiologic mechanisms underlying the variability in EE and substrate oxidation.

Thyroid hormones (THs) stimulate thermogenesis by increasing ATP consumption during TH-dependent processes (ie, substrate cycles, maintenance of ion gradients, and $Ca^{2+}$ transfer from cytosol to sarcoplasmic reticulum) and decreasing the efficiency of ATP synthesis (7). For the latter mechanism, transcriptional control of several genes, including uncoupling proteins (8) and mitochondrial glycerol-3-phosphate dehydrogenase (9), may mediate a significant fraction of TH-induced thermogenesis. THs influence lipid metabolism (10) by increasing sensitivity tosympatheticnervoussystem-mediatedlipolysis(11–13). Further-more, THs can also increase the oxidation of fatty acids by stimulating the expression of carnitine palmitoyl transferase (14).

Evidence for a significant role of THs in energy metabolism and substrate cycles comes mainly from observations made during experimental or spontaneous forms of thyroid dysfunction, which are associated with changes in energy intake, body weight and composition, macronutrient balances, body temperature, and EE. However, whether subtle differences in thyroid function within the normal range influence body weight, energy metabolism, and substrate oxidation is unclear. We explored the cross-sectional relations of plasma concentrations of thyroid-stimulating hormone (TSH) and THs with the above-mentioned variables in euthyroid, nondiabetic, adult Pima Indians and examined the relation of THs with weight change in these persons.

## SUBJECTS AND METHODS

### Subjects

The Gila River (Pima) Indian Community participates in an ongoing longitudinal study to identify risk factors for obesity and type 2 diabetes. We selected healthy nondiabetic adults who were at least three-quarters Pima or were closely related Tohono O'odham and who were euthyroid, according to normal serum TSH concentrations at admission to the clinical research unit (CRU) and retrieved from computerized laboratory records since 1997, who had measurements of energy metabolism and substrate oxidation in a respiratory chamber, and who had a nondiabetic follow-up visit with recorded weight. At this last visit, they were taking no medications that could affect weight (including antithyroidals or levothyroxine) or had a diagnosis of hypothyroidism or hyperthyroidism on review of medical records. At baseline, all subjects were admitted to the National Institutes of Health CRU of the National Institute of Diabetes and Digestive and Kidney Diseases in Phoenix, AZ, where they were fed a weight-maintaining diet (50% of calories from carbohydrate, 30% from fat, and 20% from protein) throughout their stay on the metabolic ward. Procedures were performed after ≥3 d on this diet. Subjects did not smoke or take medications at the time of the study.

All subjects gave written informed consent. The study was approved by the National Institute of Diabetes and Digestive and Kidney Diseases Institutional Review Board and the Gila River Indian Tribal Council.

## Methods

Height was measured with the use of a stadiometer; weight was obtained with an electronic digital scale. Percentage body fat (%BF) was measured by using dual-energy X-ray absorptiometry. Glucose tolerance status was assessed by using a 75-g oral-glucose-tolerance test (15). EE and substrate oxidation were assessed in a respiratory chamber (6). In brief, volunteers entered the chamber at 0745 after an overnight fast and remained therein for 23 h. Meals were provided at 0800, 1130, and 1700, and an evening snack was provided at 2000. The rate of EE was measured continuously, calculated for each 15-min interval and then averaged for the 24-h interval (24-h EE). Sleeping metabolic rate (SMR) was defined as the average EE of all 15-min periods between 2330 and 0500 during which spontaneous physical activity (assessed by a motion radar) was <1.5%. Carbon dioxide production and oxygen consumption were calculated at 15-min intervals for the 23 h in the chamber and then extrapolated to 24 h. The 24-h RQ was calculated as the ratio of 24-h carbon dioxide production to 24-h oxygen consumption. Acute energy balance (ENBAL) (ie, 24-h ENBAL during the stay in the respiratory chamber) was calculated as 24-h energy intake minus 24-h EE. On the basis of 24-h EE, 24-h RQ, and 24-h urinary nitrogen excretion, the rates for 24-h carbohydrate, lipid, and protein oxidation were calculated as previously described (16). Carbohydrate, fat, and protein balances were calculated as 24-h substrate intake minus 24-h substrate oxidation.

## Laboratory analyses

Serum TSH at the admission to the CRU was measured at the Phoenix Indian Medical Center laboratory by using a colorimetric immunoassay (Dade Behring, Newark, DE), with intraassay and interassay CVs of 3.1% and 5%, respectively. However, frozen fasting plasma samples, collected after ≥3 d on a weight-maintaining diet, were used to measure TSH, free TH, and leptin concentrations at Linco-Diagnostic Services, Inc (St Charles, MO). Plasma TSH and leptin were measured by radioimmunoassay (LincoPlex; Linco-Diagnostic Services, Inc) with intraassay and interassay CVs of 6.9% and 3% and 5.1% and 7.4%, respectively. Plasma free triiodothyrionine ($T_3$) and free thyroxine ($T_4$) concentrations were measured by using a solid-phase $^{125}I$ radioimmunoassay (Diagnostic Product Corporation, Los Angeles, CA) with intraassay and interassay CVs of 6% and 7.8% and 5% and 7%, respectively.

## Statistical analyses

**Cross-sectional analysis—**Unadjusted sex differences in plasma hormone concentrations were evaluated by Student's *t* tests and nonparametric (Kruskall-Wallis) test. Spearman's correlation analysis was used to quantify cross-sectional relations among plasma hormone concentrations, anthropometric variables, and metabolic variables. General linear regression models were used to assess independent relations of THs with 24-h EE and SMR, with both adjusted for age, sex, fat mass, and fat-free mass (FFM) (5). General linear regression models were also used to investigate the association of THs with 24-h RQ and oxidation of lipids, carbohydrates, and proteins, with all adjusted for age, sex, ENBAL, and %BF (5). Stepwise regression analysis was used afterward to estimate the individual contribution (partial $R^2$) of THs to the variance of the dependent variables.

**Prospective analysis—**Spearman's correlation analysis was used to quantify associations between THs at baseline and changes in weight. The associations were expressed as absolute changes in weight (in kg) (final weight – initial weight) or the percentage total weight change per year ({[(final weight – initial weight)/initial weight]/y of follow-up} × 100).

Statistical analyses were performed by using SAS software (version 9; SAS Institute Inc, Cary, NC). Data are expressed as means ± SDs throughout. Nonnormally distributed variables were log transformed ($\log_{10}$) before statistical analysis to approximate a normal distribution. Significance was $P < 0.05$.

## RESULTS

Subject characteristics are shown in Table 1. Neither plasma TSH nor free $T_3$ concentrations differed significantly by sex ($P > 0.3$ for both). Free $T_4$ was significantly higher in men ($P = 0.009$) and leptin was significantly higher in women ($P < 0.0001$). After adjustment for age and %BF, free $T_4$ concentrations did not differ significantly between the sexes ($P = 0.06$), and leptin concentrations remained significantly higher in women ($P = 0.002$). Although all subjects had a normal serum TSH concentration on admission (range: 0.6–4.6 $\mu$IU/mL), a few persons ($n = 10$) had plasma TSH concentrations from samples drawn several days later that were above the cutoff for normal serum values (normal ranges for plasma TSH were not available) (Figure 1).

Sex-adjusted free $T_3$ and free $T_4$ plasma concentrations were not associated with adiposity. Plasma TSH concentrations were positively associated with body weight and %BF ($r = 0.31$ and $r = 0.27$, respectively; both: $P \leq 0.01$). Plasma TSH and leptin concentrations were positively associated ($r = 0.29$, $P = 0.006$), but this association was no longer significant after adjustment for sex and %BF (partial $r = 0.15$, $P = 0.15$). Neither TSH nor leptin concentrations were associated with free $T_3$ or free $T_4$ ($P > 0.5$). Plasma concentrations of free $T_3$ and free $T_4$ were positively correlated ($r = 0.47$, $P < 0.0001$).

### Thyroid hormones, energy metabolism, and substrate oxidation

No relation was found between free $T_3$ and 24-h EE. However, in a multiple regression analysis with age, sex, fat mass, and FFM as covariates, free $T_3$ was an independent predictor of SMR (Table 2). Free $T_3$ contributed 1.2% of the total variance of SMR explained by this model. Age ($P = 0.03$) and FFM ($P < 0.001$) were additional predictors of SMR. The ratio of free $T_3$ to free $T_4$ ($T_3$:$T_4$) was also an independent predictor of SMR and explained 1.8% ($P < 0.005$) of its total variance. In regression models adjusted for age, sex, %BF, and ENBAL, free $T_3$ was an independent predictor of 24-h RQ (Table 2), contributing to 4% of its total variance. ENBAL ($P < 0.001$) was also a predictor of 24-RQ in this model. Free $T_3$ was positively and significantly associated with 24-h LOX but not with 24-h carbohydrate oxidation rate ($P = 0.004$ and $P = 0.4$, respectively). In multiple regression analysis, free $T_3$ remained associated with 24-h LOX independently of age, sex, %BF, and ENBAL (Table 2), contributing 6% of the variance explained by this model. Sex, %BF, and ENBAL (all: $P < 0.001$) were additional predictors of 24-h LOX. No significant relation was found between either TSH or free $T_4$ plasma concentration and energy metabolism or substrate oxidation.

### Total acute energy balance, substrate balances, and thyroid hormones

ENBAL was strongly correlated with fat balance (sex-partial $r = 0.69$, $P < 0.0001$) and weakly correlated with carbohydrate (sex-partial $r = 0.20$, $P = 0.06$) and protein balances (sex-partial $r = 0.23$, $P = 0.03$). A significant $y$ intercept was observed for the sex-adjusted regression line of ENBAL compared with fat and protein balances ($-177 \pm 30$ and $140 \pm 13$ kcal/d, respectively; both: $P < 0.0001$). The subjects thus tended to be in a negative fat balance and a positive protein balance when ENBAL was zero. Free $T_3$ was associated with fat (sex-partial $r = -0.27$, $P = 0.01$), carbohydrate (sex-partial $r = 0.22$, $P = 0.04$), and protein (sex-partial $r = 0.19$, $P = 0.07$) balances. However, in multiple regression analysis adjusted for age, sex, ENBAL, and %BF, free $T_3$ was an independent predictor of fat (Table 2) but not protein or carbohydrate balances ($\beta = 31$ and $\beta = 65$ respectively; both: $P = 0.15$).

### Prospective analysis

Average follow-up was $4 \pm 2$ y. During this time, the mean increase in weight was $3 \pm 9$ kg. Neither absolute nor annual percentage of changes in weight were associated with initial weight (both $P = 0.9$). Baseline $T_3$ concentrations were associated with absolute ($r = -0.23$, $P = 0.03$)

and annual (Figure 2) percentage changes in weight even after adjustment for baseline age and sex ($r = -0.27$, $P = 0.02$, and $r = -0.28$, $P = 0.009$, respectively). $T_3$:$T_4$ also showed negative but borderline ($P \leq 0.1$) associations with weight change.

## DISCUSSION

Lower concentrations of free $T_3$ predicted weight gain in euthyroid nondiabetic Pima Indians. In cross-sectional analysis, free $T_3$ but not free $T_4$ concentrations were independently associated with both SMR and LOX rate, whereas only TSH concentrations (ie, not free $T_4$ or free $T_3$) were associated with adiposity.

In patients undergoing chronic treatment with thyroxine, small changes in the daily dose, which still maintained free $T_4$ concentrations within the normal range, were associated with changes in resting EE (17). Moreover, studies in euthyroid subjects have found that serum or plasma $T_3$ concentrations were an independent predictor of 24-h EE (4), SMR (4,18), and resting metabolic rate (19). SMR, which is an accurate estimate of basal metabolic rate, is the largest component of 24-h EE and is not influenced by the thermic effect of food or the energy cost of physical activity. In the current study, free $T_3$ and free $T_3$:$T_4$ were associated with SMR, and, as in previous studies (4,18,19), they contributed (1–2%) to its variance independently of FFM. Although small, this contribution represents 5–10% (6.3% in this study) of the variance in SMR unexplained by body size, which accounts for 80–85% (81% in this study) of the EE variance (5).

In agreement with a previous report (20), 24-h ENBAL was strongly correlated only with net fat balance, which indicated that even a small degree of overfeeding on a mixed diet would result mostly in fat storage. Indeed, a lower LOX rate, which predisposes to a positive fat balance, is a predictor of weight gain (2,3). The association found between free $T_3$ and 24-h RQ, a ratio of carbohydrate oxidation rate to LOX rate, has not been reported previously in euthyroid persons. This negative relation was explained by the positive and independent association of free $T_3$ with LOX rate and the lack of association with carbohydrate oxidation. Because lower EE is also a risk factor for weight gain (1), it is not surprising that free $T_3$, which was a predictor of both SMR and LOX rate, predicted changes in body weight in this population.

In this study, TSH but not free $T_3$ or free $T_4$ was associated with adiposity. Free TH concentrations, which are unaffected by factors modifying serum-binding proteins, were reported to be positively (21), negatively (22–25), or not (21,22,26–28) associated with adiposity. Two large cross-sectional studies showed a positive association between circulating TSH and adiposity (24,29). Spontaneous 24-h TSH secretion was also enhanced in obese compared with lean women (27). Some animal (30,31) and human (27,32) studies indicate that leptin may mediate this association. The increased activity of the hypothalamic-pituitary-thyroid axis in response to increasing leptin concentrations could act as a check against further weight gain, in part through the metabolic effects of THs. However, leptin administration failed to increase TSH concentrations in both healthy adults (33) and children with congenital leptin deficiency (34). In this study, we observed no association between leptin and TSH after adjustment for adiposity, and no association was observed between adiposity, TSH, and leptin or free TH concentration, as would have been expected under the above hypothesis. Therefore, mechanisms other than leptin may contribute to increased TSH concentrations in obese people.

In this study, free $T_3$ but not free $T_4$ concentrations were associated with metabolic variables and predicted weight change. $T_4$, the main product of thyroid secretion, must be activated by deiodination to the biologically active hormone $T_3$ by type 1 deiodinase (D1) or type 2 deiodinase (D2). Free $T_3$:$T_4$ is considered an estimate of deiodination activity. D2 is a selenoenzyme mainly expressed in the central nervous system, pituitary and thyroid glands,

skeletal muscle, and adipose tissue (35). A complex control of D2 activity is critical for the $T_4$-mediated negative feedback in thyrotrophic cells (36). D2 is also a main determinant of both nuclear TH receptor-bound $T_3$ (37) and plasma $T_3$ concentrations in euthyroid humans (38). Therefore, a decrease in D2 activity in metabolically active tissues (such as adipose or muscle tissue) could explain the observed association of free $T_3$ concentrations with SMR, LOX, and weight change. This decrease in central D2 activity may affect the feedback mechanism so that a slight decrease in intracellular $T_3$ would promote an increase in TSH secretion, and that may explain the lack of association between TSH and free $T_4$ concentrations in our subjects. Factors modifying D2 activity beside $T_4$ concentrations (38) have not been clearly identified. However, genetic polymorphisms of the D2 gene, which were not associated with TH concentrations in this study (data not shown; 39, 40), deficiency in selenium (41) or alterations in its incorporation into D2 (42), oxidative stress (43), inflammation (44), and nutritional factors (45–48), can modify D2 activity. Although D2 may play an important role in these associations, D1, which is both an activating and deactivating enzyme and which contributes to serum $T_3$ concentrations (38,49), and D3 (an inactivating enzyme) may also play a significant role in these associations.

On the basis of the cross-sectional associations, we have speculated about a possible effect of lower free $T_3$ concentrations on weight gain through a decrease in resting EE and LOX rate. However, SMR and 24-h LOX were not predictors of weight change in this population (data not shown), and adjustment for these variables did not modify the association of baseline free $T_3$ concentrations and weight change. This finding could be due to differences in the ability to measure SMR and 24-h LOX (greater interindividual variability or less accuracy) compared with free $T_3$ concentrations, or it may indicate that other mechanisms, including energy intake and levels of physical activity and its energy cost, mediate the association of free $T_3$ with body weight gain. Furthermore, sympathetic nervous system activity is a confounder not accounted for in this study. Sympathetic nervous system activity predicts weight change (50), stimulates the peripheral conversion of $T_4$ to $T_3$ (51–53), and inhibits food intake (54). THs are involved in multiple processes; therefore, the effects of TH on weight gain may occur by the additive effect of several mechanisms rather than by a modulation of a single fundamental process.

A normal serum TSH concentration, measured on the day of the admission, was our inclusion criterion to study only euthyroid persons. However, plasma TSH concentrations, measured ≥3 d after stabilization with a weight-maintaining diet, were found to be slightly elevated in some of the subjects ($n = 10$), according to the upper cutoff established for serum TSH concentrations. Differences in the assay, type of sample used (plasma compared with serum), intraindividual variability over time, and time of venipuncture are factors that could explain this discrepancy (55). Subjects with this mild elevation in plasma TSH, however, had normal free $T_4$ and free $T_3$ concentrations. When they were excluded from the analysis, results did not change (data not shown).

Although our data show that low $T_3$ concentrations are associated with weight gain, it is important to acknowledge that, because of its cardiovascular and protein-wasting effects, TH treatment is not a safe strategy in a pharmacologic approach to the problem of obesity. Whether tissue-selective (specifically, muscle) modifications in deiodinase activity may be a suitable target for drug intervention remains unclear (56). It is intriguing, however, that supplementation of a high-fat diet with bile acids increased thermogenesis by the selective activation of D2 in brown adipose tissue (the thermogenic organ in mice) and that it protected these mice from the obesigenic effect of this diet (48).

In summary, free $T_3$ but not free $T_4$ plasma concentrations are associated with SMR, LOX rate, and weight change in euthyroid adult persons. This finding indicates that factors influencing the conversion of $T_4$ to $T_3$ could play a role in energy homeostasis and body weight regulation.

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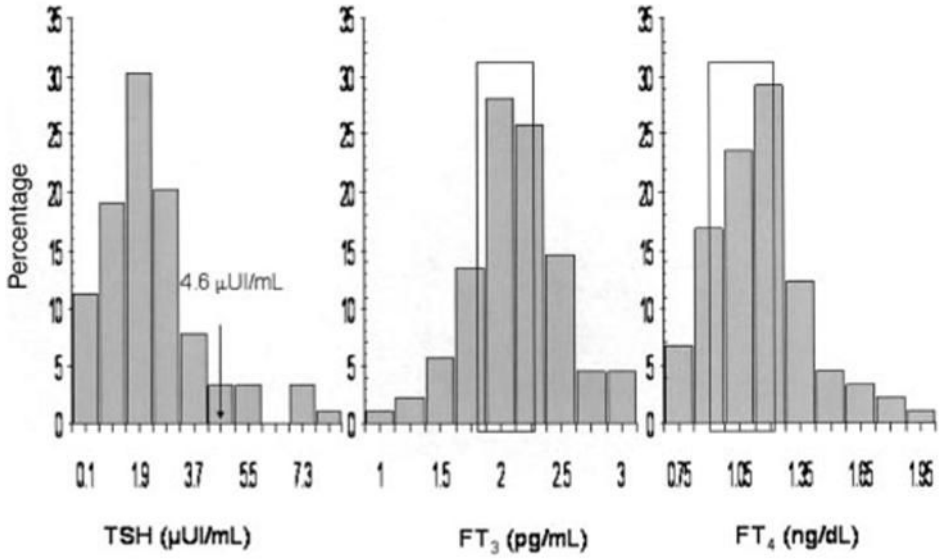


**FIGURE 1.**
Distributions of plasma concentrations of thyroid-stimulating hormone (TSH), free triiodothyronine ($FT_3$), and free thyroxine ($FT_4$) in 89 persons. $FT_3$ and $FT_4$ concentrations in subjects with plasma TSH concentrations above the normal range for serum TSH (ie, 4.6 $\mu$UI/mL; $n$ = 10) were within the limits indicated in the figure (boxes) and above the 25th and 10th percentiles of the study population, respectively.

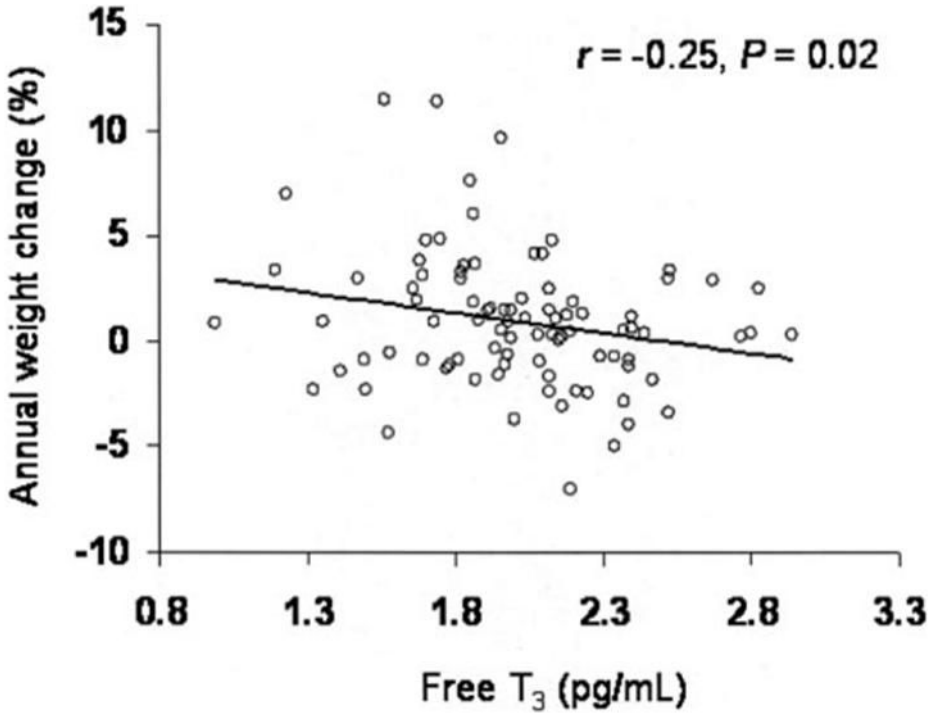


**FIGURE 2.**
Relation between baseline free triiodothyronine ($T_3$) concentrations and weight change in 89 persons. Spearman's simple correlation coefficient and *P* value for the association of free $T_3$ ($\bar{x} \pm$ SD: 2 ± 0.4 pg/mL) and annual percentage of weight change ($\bar{x} \pm$ SD: 1 ± 3%) are given.

## TABLE 1

Subject characteristics[1]

| Characteristics | Value |
|---|---|
| Sex | |
| Females (*n*) | 42 |
| Males (*n*) | 47 |
| Glucose tolerance | |
| Normal (*n*) | 60 |
| Impaired (*n*) | 29 |
| Age (y) | 29 ± 7 (18–44)[2] |
| Height (cm) | 167 ± 7 (152–183) |
| Body weight (kg) | 93 ± 20 (55–137) |
| Percentage body fat (%) | 33 ± 7 (14–46) |
| Fat-free mass (kg) | 61 ± 11 (41–85) |
| Fasting glucose (mg/dL) | 87 ± 9 (64–116) |
| 2-h OGTT (mg/dL) | 121 ± 30 (51–197) |
| Fasting insulin ($\mu$U/mL) | 44 ± 18 (13–112) |
| TSH ($\mu$IU/mL) | 2.75 ± 1.69 (0.35–8.94) |
| Free $T_3$ (pg/mL) | 2 ± 0.4 (1–2.94) |
| Free $T_4$ (ng/dL) | |
| Males | 1.3 ± 0.3 (0.78–1.97) |
| Females | 1.1 ± 0.2 (0.71–1.55) |
| Leptin (ng/mL) | |
| Males | 9.6 ± 4.9 (1.8–21.2) |
| Females | 28.9 ± 10.6 (4.4–45.7) |
| 24-h Energy expenditure (kcal/d) | 2340 ± 385 (1545–3332) |
| Sleeping metabolic rate (kcal/d)[3] | 1642 ± 230 (1164–2164) |
| 24-h Respiratory quotient | 0.85 ± 0.02 (0.8–0.9) |
| 24-h Carbohydrate oxidation (kcal/d) | 1113 ± 219 (549–1677) |
| 24-h Lipid oxidation (kcal/d) | 936 ± 267 (431–1729) |
| 24-h Energy balance (kcal/d) | −162 ± 222 (−745 to 286) |
| 24-h Carbohydrate balance (kcal/d) | −23 ± 163 (−414 to 503) |
| 24-h Fat balance (kcal/d) | −282 ± 236 (−1069 to 149) |
| 24-h Protein balance (kcal/d) | 164 ± 99 (−58 to 475) |

[1] $n$ = 89. TSH, thyroid-stimulating hormone; OGTT, oral-glucose-tolerance test; $T_3$, triiodothyronine; $T_4$, thyroxine. Insulin ($\mu$UI/mL), glucose (mg/dL), TSH ($\mu$IU/mL), free $T_3$ (pg/mL), and free $T_4$ (ng/dL) concentrations are given in conventional units; to convert to SI units (pmol/L, mmol/L, $\mu$IU/L, pmol/L, and pmol/L, respectively), multiply by 6.945, 0.055, 1, 1.54, and 12.87, respectively.

[2] $\bar{x}$ ± SD; range in parentheses (all such values).

[3] Data available for 86 subjects.

## TABLE 2

Adjusted association between free triiodothyronine ($T_3$) concentrations and metabolic variables by general linear regression analysis in 89 subjects[1]

| | SMR[2] | | 24-h RQ[3] | | 24-h LOX[4] | | Fat balance[5] | |
|---|---|---|---|---|---|---|---|---|
| | β | P | β | P | β | P | β | P |
| Free $T_3$ | 74.4 | 0.02 | −0.01 | <0.05 | 126 | 0.006 | −132 | 0.004 |

[1] Data are $\beta$ (estimated partial regression coefficient) and $P$ values for the association of free T3 concentrations ($\bar{x}$ ± SD: 2 ± 0.4 pg/mL) with metabolic variables after adjustment for covariates. SMR, sleeping metabolic rate; RQ, respiratory quotient; LOX, lipid oxidation.

[2] Data available in 86 subjects. SMR (1642 ± 230 kcal/d) adjusted for age, sex, fat mass, and fat-free mass. Total $R^2$ = 0.83 and $P$ < 0.0001 for the entire model.

[3] RQ (0.85 ± 0.02) adjusted for age, sex, percentage body fat, and energy balance. Total $R^2$ = 0.28 and $P$ < 0.0001 for the entire model.

[4] LOX (936 ± 267 kcal/d) adjusted for age, sex, percentage body fat, and energy balance. Total $R^2$ = 0.49 and $P$ < 0.0001 for the entire model.

[5] Fat balance (−282 ± 236 kcal/d) adjusted for age, sex, percentage body fat, and energy balance. Total $R^2$ = 0.55 and $P$ < 0.0001 for the entire model.