Lean Body Mass is a Predictor of the Daily Requirement for Thyroid Hormone in Older Men and Women

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Levothyroxine (T_4) replacement need in adults with primary hypothyroidism has recently been reported to fall with age. Previous studies have demonstrated that the resting metabolic rate falls with age in euthyroid adults and that this fall is proportional to a reduction in lean body mass (LBM). Since LBM is correlated also with 24-hour energy expenditure, this study examined the possibility that LBM might be an accurate predictor of T_4 requirement. Seventy-five hypothyroid adults receiving full replacement therapy, ranging in age from 24 to 88 years, were studied retrospectively. Lean body mass was found to be a better predictor of T_4 requirement than age or weight for the entire group as well as for subgroups of men and women 51 years old and older. The age-related reduction in LBM may be responsible for the reported decrease in the rate of fractional thyroxine degradation with age.

A reduction in resting metabolic rate (RMR), determined by indirect calorimetry, is a classic manifestation of hypothyroidism.[1] Indeed, basal metabolism was used to assess the adequacy of the replacement dose of thyroid extract in hypothyroidism as early as 1921.[2] The RMR has been shown to fall with age in euthyroid adults,[3–7] and this age-related fall in RMR has been demonstrated to be proportional to a reduction in lean body mass (LBM).[8,9] LBM, which presumably reflects the mass of actively metabolizing tissue cells[10] is highly correlated not only with RMR[11,12] but also with 24-hour energy expenditure independently of age.[12,13] Unlike body surface area or body weight indices, LBM removes sex effects from RMR.

An age-related decrease in the levothyroxine (T_4) requirement of adults with primary hypothyroidism, based on the normalization of circulating thyroid stimulating hormone (TSH) levels, has been reported by Davis et al;[14] Sawin et al.,[15] and Rosenbaum and Barzel.[16] In the latter study, the levothyroxine dose correlated with either weight ($r = 0.60$, $P < 0.0001$) or age ($r = -0.48$, $P < 0.0001$). Since age and weight are major factors influencing LBM, we speculated that LBM might be an accurate predictor of levothyroxine replacement need in adults with primary hypothyroidism. A significant correlation between T_4 replacement and LBM could suggest that the mass of lean tissue determines both T_4 hormone requirement and RMR in euthyroid adults.

A retrospective analysis of data for 75 hypothyroid patients receiving full replacement therapy, including the subjects of Rosenbaum and Barzel,[16] was performed to examine this hypothesis.

METHODS

Seventy-five adults with documented hypothyroidism, receiving full thyroid replacement therapy, were studied. There were 66 women and nine men, a ratio reflecting the female predominance of this disease. Of the women, 44 were 51–88 years old and 22 were 24–50 years old. All nine men were older than 51 years, ranging from 53 to 82 years of age. (There were only four men younger than 50, two of them very obese, in the original group of Rosenbaum and Barzel.[17] These were excluded from this study). The age and weight at full replacement for each patient were used to estimate lean body mass[11] from formulas of total body water.[18]

Male

$$LBM = (79.5 - 0.24M - 0.15A) \times M \div 73.2$$

Female

$$LBM = (69.8 - 0.26M - 0.12A) \times M \div 73.2$$

where M = body weight in kg and A = age in years. Analysis of the data was by least-squares regression and Student's *t*-test.

RESULTS

The mean age, weight, LBM, and T_4 replacement dose of the entire patient data set are given

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in Table 1. Since the majority of the patients were women, their data are listed separately as well. Multiple regression analysis showed a significant multiple correlation for T_4 versus these three variables ($r = 0.56$, $F = 10.6$). Table 2 summarizes the regression analyses of T_4 replacement as predicted by estimated LBM, age, or weight for all patients as well as various subgroups. Significant correlations were found in each regression for the entire patient group.

Estimated LBM was the best single predictor for T_4 replacement dose ($r = 0.50$, $F = 24.7$, $P < 0.001$). The least square prediction equation is:

$$T_4\ (\mu g/day) = 3.4 \times LBM - 11$$

with the standard error of estimate being 39 μg/day.

When analyzed separately for the nine men, the correlation of LBM with T_4 replacement dose was high ($r = 0.58$, $0.10 > P > 0.05$). (Inclusion of the four younger men markedly improved the correlation of LBM with T_4 for men [n = 13, $r = 0.90$]). For the entire female group (Table 2), both LBM and age provided equal predictive ability ($F > 15$). The multiple regression with all three variables was not better ($r = 0.50$, $F = 7.1$). The regression lines and prediction equations for T_4 on LBM and for T_4 on age are both depicted in Figure 1. The regression of T_4 on LBM has an intercept near zero (−12 μg/day) and a slope that is 2.5 times greater that that for T_4 on age.

Further analysis of the data revealed that in women aged 50 or younger there was no correlation of T_4 with LBM ($r = 0.09$) or age ($r = 0.12$). There was, however, a highly significant correlation between T_4 and LBM ($r = 0.47$, $P < 0.001$) for the older women. Combining the data for the older women with that of the men (who were all older than 51) improves the correlation of T_4 with LBM ($r = 0.62$, $P = < 0.001$) and, to a lesser extent, that with age as well ($r = -0.31$, $P < 0.05$) (Table 2).

Regression equations of T_4 on LBM for the entire group and various subgroups are provided in Table 3.

TABLE 1
*Population Parameters of 75 Adult Hypothyroid Patients**

Characteristic	All Patients (n = 75)	Women Only (n = 66)
Age (years)	60 ± 1.8	59 ± 2.0
Weight (kg)	70 ± 1.8	69 ± 1.9
Lean body mass (kg)	43 ± 0.8	42 ± 0.7
T_4 (μg/day)†	134 ± 5.2	130 ± 5.5

* All values are mean + SEM.
† Full replacement dose.

DISCUSSION

Thyroxine replacement was shown by regression analysis to be significantly correlated with the three variables—age, weight, and LBM—examined in our hypothyroid patients. Lean body mass was the best predictor of T_4 replacement for the entire population or for the men plus women who were 51 years of age or older. Age and LBM were both equally good in estimation of T_4 requirement in the hypothyroid female population as a whole. However, as shown in Figure 1, the regression line of T_4 requirement on LBM had an intercept which was nearer zero, which is to be expected theoretically if T_4 in adults depended solely on LBM. Furthermore, the 2.5-fold greater slope indicates that LBM is a more sensitive predictor of T_4 requirement than age, given an equal correlation and standard error of estimation. The retrospective estimation of LBM does not prove a precise estimation of T_4 replacement (the 95 per cent confidence interval is ± 80–83 μg/day). However, the correlation of estimated LBM with T_4 replacement suggests that the decrease in T_4 need reported for older hypothyroid patients[14–16] may be explained by age-related changes in body composition. The reduction in lean body mass that is known to occur with age may be responsible for the observed decrease in fractional thyroxine degredation rate with age.[19]

The correlation of complete physiologic replace-

TABLE 2
*Correlation Coefficients for Predictors of T_4 Replacement**

Variable	All Patients (n = 75)	Men (n = 9)	All Women (n = 66)	Older Women (n = 44)	Older Women and Men (n = 53)
Lean body mass	0.50†	0.58‡	0.45†	0.47†	0.62†
Age	−0.40†	−0.58‡	−0.44†	−0.27	−0.31§
Weight	0.37†	0.40‡	0.34‖	0.43‖	0.45†

* All values as r for T_4.
† $P < 0.001$.
‡ $P > 0.05$.
§ $P < 0.05$.
‖ $P < 0.01$.

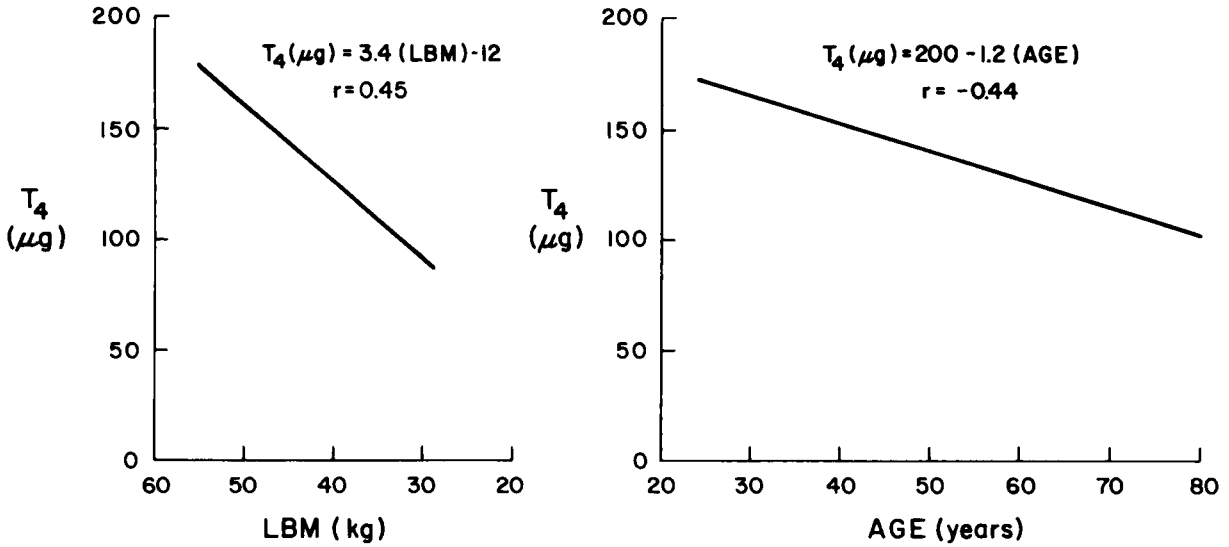

Figure 1. Regression of daily levothyroxine replacement dose (T_4) on lean body mass (LBM) and on age in 66 hypothyroid women. To facilitate comparison, LBM is plotted as a decreasing mass along its axis; LBM decreases with increasing age ($r = -0.57$) in these subjects. The limits for 95 per cent confidence in predicting an individual T_4 replacement from either LBM or age are ± 80–83 micrograms per day.

TABLE 3
Regression of T_4 Replacement Dose on Lean Body Mass (LBM) in Hypothyroid Adults

Group	n	r	Equation for T_4 (μg/day)
All	75	0.50	3.4 × LBM − 11
Men only	9	0.58	3.9 × LBM − 40
Women only	66	0.45	3.4 × LBM − 12
Older women	44	0.45	3.3 × LBM − 10
Older women and men	53	0.62	3.6 × LBM − 30
Younger women	22	0.09	—

ment of T_4 with LBM provides evidence that the dose is adjusted to daily energy expenditure as well.[12,13] This is the case for men and women older than 50. In this age group, no sex effect per se is evident, which is consistent with the notion that the mass of actively metabolizing cells regulates T_4 demand.

The distinct lack of correlation in the group of younger women cannot be explained by our data. We may conjecture that T_4 metabolism is influenced in the premenopausal state by some factors such as steroid hormones that play a diminishing role in the postmenopausal state. Further studies of pre- and postmenopausal women, and of younger men, will be required to clarify this question.

A direct assessment of LBM would be preferable, in such studies, to the retrospective estimation used here. Available methods to be considered include several tracers for total body water, body fat from densitometry or skinfold thickness, or total body potassium estimation.[20] Of these, determination of potassium space or a combination of potassium space and body water are probably the procedures of choice when normohydration cannot be assumed, as in myxedema. Skinfold thickness estimation for total fat may be less useful, especially in the elderly,[21] despite its refractivity to changes in the state of hydration. Longitudinal studies of coincident changes in LBM, energy expenditure, and T_4 requirement for complete replacement may provide valuable insight into the physiologic basis of the progressive decline of all three parameters with age. Recent advances in indirect calorimetry, primarily through the use of the "ventilated hood" technique, insure accurate measurement of RMR[22] in such a study.

Clinically, assessment of the LBM may allow optimization of thyroxine replacement in older patients in whom TSH estimation is impossible, such as those with pituitary disease and secondary hypothyroidism.

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