0021-972X/05/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 90(1):124–127

doi: 10.1210/jc.2004-1306

Lean Body Mass Is a Major Determinant of Levothyroxine Dosage in the Treatment of Thyroid Diseases

Ferruccio Santini, Aldo Pinchera, Alessandro Marsili, Giovanni Ceccarini, Maria Grazia Castagna, Rocco Valeriano, Monica Giannetti, Donatella Taddei, Roberta Centoni, Giovanna Scartabelli, Teresa Rago, Claudia Mammoli, Rossella Elisei, and Paolo Vitti

Department of Endocrinology, University of Pisa, 56124, Pisa, Italy

Total body weight is usually employed to calculate the amount of L-T_4 to be administered in patients with thyroid diseases. The aim of this study was to evaluate the effect of body composition on L-T_4 requirements. Body composition was assessed by dual energy x-ray absorptiometry in 75 patients on TSH-suppressive L-T_4 therapy after conventional thyroid ablation for differentiated cancer. The mean daily dose of L-T_4 was lower in normal-weight (127.5 ± 21.3 μg/d) *vs.* overweight (139.4 ± 24.5) and obese (151.3 ± 29.1) subjects. There was a much stronger association between the L-T_4 dosage and lean body mass ($P < 0.001$, $r = 0.667$) compared with fat mass ($P = 0.023$, $r = 0.26$). Measurement of regional tissue composition showed peripheral lean mass as the best correlate with the dose of L-T_4 ($r = 0.679$, $P < 0.001$) whereas no correlation was observed with peripheral fat mass. In conclusion, individual L-T_4 requirements are dependent on lean body mass. Age- and gender-related differences in L-T_4 needs reflect different proportions of lean mass over the total body weight. An estimate of lean mass may be helpful to shorten the time required to attain a stable dose of L-T_4, particularly in subjects with high body mass index values that may be due either to increased muscular mass or to obesity. (*J Clin Endocrinol Metab* 90: 124–127, 2005)

LEVOTHYROXINE (L-T_4) IS commonly employed to correct thyroid hormone deficiency from various causes (1–4) or to reduce serum concentrations of TSH in the management of thyroid cancer (5–7) or nodular goiter (8–9). Both excess and insufficient thyroid hormone produce adverse effects in various tissues (10–13), and careful monitoring is advisable to establish the optimal dose of L-T_4 (14). Beside clinical evaluation, the sensitive immunometric TSH assays currently available allow precise L-T_4 dosage in most patients (15). Nevertheless, substantial interindividual variations of L-T_4 requirements occur depending on the patient's age, gender, and body size (1–4, 16–18). The presence of residual functioning thyroidal tissue, concurrent nonthyroidal diseases (2–3), pharmacological agents (19), or specific physiologic conditions, such as pregnancy (20), may also call for adjustment of the L-T_4 daily dose. There is a general agreement in literature that ideal body weight should be considered to calculate the amount of L-T_4 to be administered in each patients, and evidence has been provided (21) that lean body mass is a predictor of the daily requirements for thyroid hormone in the elderly. Yet, the influence of overweight and obesity on the management of L-T_4 therapy has not been fully elucidated. This study was undertaken to evaluate the effect of body composition, as assessed by dual energy x-ray absorptiometry (DEXA), on L-T_4 requirements in a group of thyroidectomized patients on TSH-suppressive L-T_4 therapy.

First Published Online October 13, 2004

Abbreviations: BMI, Body mass index; DEXA, dual energy x-ray absorptiometry; fT_3, free T_3; fT_4, free T_4.

Patients and Methods

Patients

Seventy-five patients (52 females, 23 males) turning to our Endocrine Unit were enrolled after total thyroidectomy and ^{131}iodine remnant ablation for differentiated thyroid cancer. According to current criteria for the management of thyroid cancer (22), they were apparently free of disease. In particular, basal and recombinant human TSH-stimulated serum thyroglobulin and antithyroglobulin antibody were undetectable, indicating no functioning thyroid tissue at the time of the study. Patients had been on suppressive doses of L-T_4 [serum TSH 0.005–0.3 mU/liter, free T_4 (fT_4) and free T_3 (fT_3) within their normal ranges] for more than 6 months, without interruptions or dose adjustments during this time period. They were not taking medications known to influence thyroid hormone adsorption or metabolism, and they did not have concurrent nonthyroidal diseases at the time of the study. L-T_4 was taken in the fasting state. Patients were assigned to one of three subgroups based on their body mass index (BMI): normal weight (BMI 18.5–24.9 kg/m^2); overweight (BMI 25–29.9) and obese (BMI ≥ 30). In each subgroup, the enrollment was consecutive until 25 patients/subgroup were recruited. This enrollment criterion was followed to ensure an even distribution of various anthropometric measures within our study group. The clinical characteristics of patients from the three subgroups are shown in Table 1. Informed consent was obtained from all patients.

Serum assays

Blood morning samples were obtained 24 h after the last ingestion of L-T_4. Serum TSH was measured by the chemoluminescent method (Immulite 2000, DPC, Los Angeles, CA). Serum free T_4 (fT_4) and fT_3 were measured by immunometric method (Vitros, Ortho-Clinical Diagnostic, Rochester, NY). Normal values in our laboratory are as follows: TSH, 0.4–3.4 mU/liter; fT_4, 7–17 pg/ml (9.0–21.9 pmol/liter); and fT_3, 2.7–5.7 pg/ml (4.15–8.75 pmol/liter). Serum thyroglobulin antibody was as-

TABLE 1. Anthropometric measures, L-T_4 daily dose, and serum hormonal concentrations in the three subgroups of patients (25 patients/subgroup)

	Normal weight	Overweight	Obese
Weight (kg)	61 ± 7.5	78 ± 10.0[a]	93 ± 13.5[a,b]
Height (cm)	166 ± 8	167 ± 10	166 ± 10
BMI (kg/m^2)	22 ± 1.7	27.9 ± 1.6[a]	33.6 ± 3.0[a,b]
Age (yr)	39 ± 11	43 ± 12	49 ± 10[a]
L-T_4 dose (μg/d)	127.5 ± 21.3	139.4 ± 24.5	151.3 ± 29.1[a]
L-T_4 dose (μg/kg·d)	2.10 ± 0.31	1.80 ± 0.31[a]	1.63 ± 0.22[a,b]
Serum fT_4 (pmol/liter)	17.5 ± 2.2	17.2 ± 2.7	17.7 ± 2.2
Serum fT_3 (pmol/liter)	5.72 ± 0.61	6.03 ± 0.50	5.86 ± 0.77
Serum TSH (mU/liter)	0.069 ± 0.056	0.091 ± 0.089	0.068 ± 0.061

Data are reported as mean ± SD.

Differences among subgroups were analyzed by Student's *t* test for unpaired variates: [a] $P < 0.05$ *vs.* normal weight; and [b] $P < 0.05$ *vs.* overweight. To convert fT_4 and fT_3 to picograms per milliliter, multiply by 0.777 and 0.651, respectively.

sayed by an immunoradiometric assay method (ICN Pharmaceuticals Inc., Asse Relegem, Belgium). Serum thyroglobulin was measured using a commercial chemoluminescent immunometric assay (DPC). Serum leptin was assayed by an RIA kit (Linco Research, St. Charles, MO).

Evaluation of body composition

Total and regional lean body mass and fat body mass were measured by DEXA (Hologic QDR 4500A, Hologic Inc. Walthan, MA). DEXA scans were analyzed with the manufacturer's whole-body version (Hologic Inc.). Peripheral values of lean and fat mass were calculated by adding up values measured in superior and inferior limbs.

Results

As shown in Table 1, our study group ranged over a broad interval of body weight (46–123 kg) and BMI (19.1–40.4 kg/m^2). Mean age was significantly lower in normal-weight as compared with obese subjects, reflecting the lower prevalence of obesity in young *vs.* middle-aged adults. The mean total daily dose of L-T_4 increased in overweight and obese subjects as compared with normal-weight subjects, but the dose per kilogram was significantly reduced going from lean toward obese subjects. There were no significant differences in serum fT_4, fT_3, and TSH concentrations among the three subgroups. Furthermore, there was no association between the total daily dose of L-T_4 and serum fT_4, fT_3, or TSH concentrations, as assessed by linear regression in the whole group (data not shown).

The relationship between the total daily dose of L-T_4 and body composition was analyzed by simple linear regression (Fig. 1). As expected, there was a significant positive correlation between the L-T_4 dose and total body weight ($P < 0.001$, r = 0.611). The association was much stronger when the L-T_4 dose was correlated with lean body mass ($P < 0.001$, r = 0.667) than with fat mass ($P = 0.023$, r = 0.26), both measured by DEXA. Confirming the poor role of fat mass in determining the L-T_4 requirement, no association was observed between L-T_4 daily dose and serum leptin concentration. The mean total daily dose of L-T_4 was significantly higher in male than in female patients (160 ± 29 *vs.* 130 ± 20 μg/d, respectively; $P < 0.001$ as assessed by Student's *t* test), but there was no difference when the daily dose of L-T_4 was corrected for body weight (1.76 ± 0.10 *vs.* 1.88 ± 0.12 μg/kg·d, respectively). Thus, as evident from Fig. 1, the gender-related variations of L-T_4 requirement appear dependent on differences in total body weight, with lean mass content having the highest impact.

Measurement of regional tissue composition showed peripheral lean mass as the best correlate with the total daily dose of L-T_4 (r = 0.679, $P < 0.001$), whereas no association was found between L-T_4 dose and peripheral fat mass (Fig. 2). A weaker correlation was found between the total daily dose of L-T_4 and trunk lean (r = 0.484, $P < 0.001$) or fat (r = 0.243, $P = 0.036$) masses.

A significant negative correlation was observed between patients' age and the L-T_4 daily dose corrected for body weight (r = 0.25, $P = 0.03$). This relationship disappeared when the L-T_4 daily dose was corrected for lean body mass, indicating that the age-related reduction of L-T_4 requirements is associated to a decrease in lean body mass.

Discussion

A stable dose of L-T_4 in treatment of thyroid diseases is achieved when the amount of hormone entering the bloodstream equals the proportion that is metabolized, allowing constant serum concentrations of fT_4, fT_3, and TSH. When administered in the fasting state, about 80% of L-T_4 contained in modern tablets is absorbed (23). After ingestion, serum T4 values peak at 2–4 h and return toward basal levels after about 6 h. The serum half-life of T4 approximates 7 d in the euthyroid state, and its clearance depends mainly on deiodination and to a lesser extent on other pathways, such as sulfation and glucuronidation (24). The daily replacement dose of L-T_4 to normalize serum TSH in adult hypothyroid subjects is, on average, 1.6 μg/kg. The amount of hormone to be administered must be increased when suppressed values of serum TSH are desired. In both cases, however, individual adjustments are usually required to attain the optimal daily dose. Although the total daily requirements of L-T_4 are related to body mass, unexplained difference can occur among individuals for the same age and body size, even in the absence of functioning thyroid tissue. In this regard, the role of obesity in affecting L-T_4 disposal and therapy requirements has never been defined.

To gain further insights into the influence that body composition may exert on L-T_4 therapeutical needs, we have studied a group of hypothyroid patients who had been totally ablated for thyroid cancer and had been placed on L-T_4 at TSH suppressive doses. The advantages of this selection are: no functioning residual thyroid tissue, narrow ranges of serum thyroid hormones and TSH on L-T_4 therapy, and good compliance to drug prescription, which is usually obtained in neoplastic patients under a strict follow-up. Although L-T_4 therapy was care-

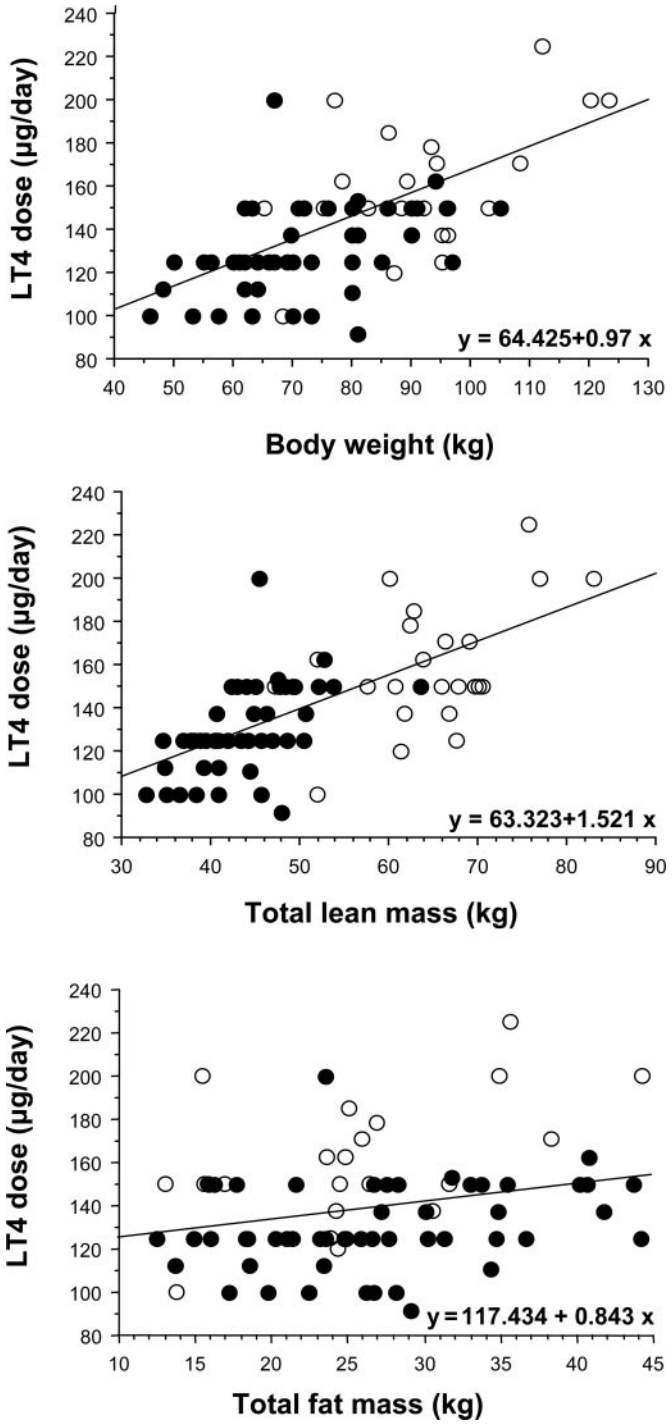

FIG. 1. Correlations between the daily dose of L-T_4 and total body weight (*upper panel*), total lean mass (*middle panel*), or total fat mass (*lower panel*) in 75 thyroidectomized patients on L-T_4 therapy at TSH-suppressive doses. *Open circles*, Males; *filled circles*, females.

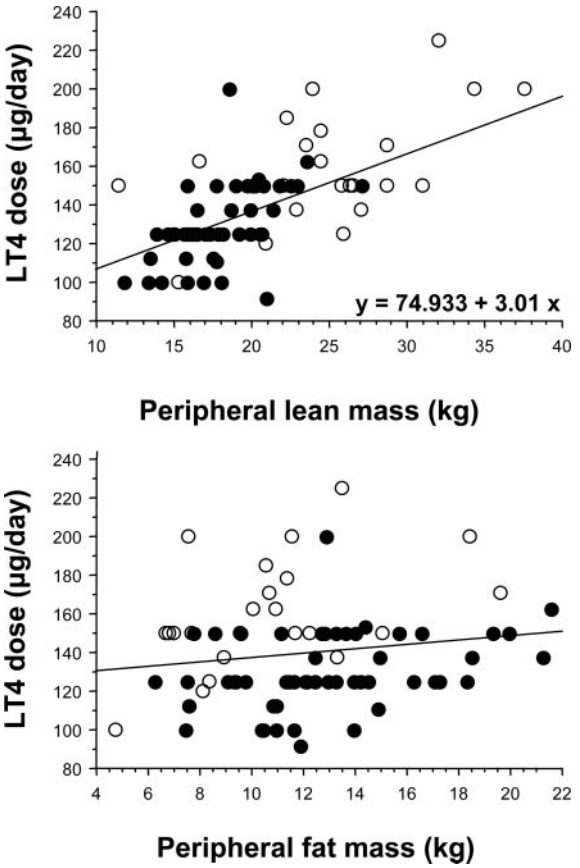

FIG. 2. Correlations between the daily dose of L-T_4 and peripheral lean mass (*upper panel*) or peripheral fat mass (*lower panel*) in 75 thyroidectomized patients on L-T_4 therapy at TSH-suppressive doses. *Open circles*, males; *filled circles*, females.

fully carried out and monitored, using the smallest dose required to suppress TSH secretion, it is possible that the slight thyroid hormone excess, necessary to reduce serum TSH, may introduce a limitation. In this regard, however, current evidence indicates that body composition is not affected in patients taking TSH-suppressive doses of L-T_4 as compared with healthy controls (25). Body composition was analyzed by DEXA that allows precise and reproducible measures of total as well as regional fat mass and lean mass (26–27).

On one hand, the results of our study suggest that excessive fat accumulation, as indicated by increased BMI values, would imply higher doses of L-T_4 to attain the same TSH reduction as in lean subjects (Table 1). On the other hand, after looking at body composition, lean body mass appears as the best correlate of L-T_4 daily requirements, whereas fat mass has little or no effect. This observation implies that T4 disposal mainly occurs within the lean compartment. Leptin is specifically produced by adipocytes and serum leptin concentrations are proportional to the amount of total adipose tissue (28). The absence of correlation between serum leptin and the total L-T_4 administered to our patients confirms that the adipose tissue has a minor impact on L-T_4 needs. Lean body mass has been shown to be superior to other measures of body size as a predictor of dosage for many drugs (29). This may not be surprising considering that most metabolic processes occur within this body compartment. In case of thyroid hormone, type 3 inner-ring deiodination, converting T_4 to inactive reverse T_3, has been demonstrated in skin, which accounts for a large proportion of lean body mass in humans (30). Furthermore, type 2 outer-ring deiodinase enzyme, converting T_4 to T_3, has been detected in skeletal muscle, making this tissue an important site for T_4 degradation (31). The relevance of skin and skeletal muscle in T_4 degradation was strengthened by our finding that lean mass in extremities, as a

predictor of L-T_4 daily dose, is superior to whole-body or trunk lean masses that include the visceral component. However, the total lean mass also correlates with liver volume and liver blood flow, and a good relationship has been observed between lean body mass and drug clearance for several pharmacological agents that are metabolized predominantly by the liver (29). Because several pathways of T_4 metabolism take their place in liver, including type 1 outer-ring deiodination, sulfation, and glucuroconjugation (24), it is presumable that the relationship between L-T_4 dosage and lean body mass partially reflects the hepatic contribution to L-T_4 clearance. Lean body mass has been found to be a better determinant of thyroid volume than body weight, both in normal-weight and obese subjects (32). This observation is in line with our findings; taken together, these results indicate that requirements for T_4, either secreted by the thyroid or therapeutically administered, depend on lean body mass.

According to the role of lean mass in determining L-T_4 disposal, the absolute value of L-T_4 requirement was higher in males than in females, as a consequence of gender-related differences in body weight and body composition. Finally, confirming previous studies (21), the well-known reduction of L-T_4 needs associated to advancing age appeared dependent on a relative decrease in lean body mass.

We conclude that individual requirements of L-T_4 in subjects receiving hormonal therapy for thyroid diseases are greatly dependent on the respective lean body mass and that age- and gender-related differences in L-T_4 needs reflect different proportions of lean mass over the total body weight. Although individual monitoring of clinical and hormonal parameters remains essential for proper adjustment of the L-T_4 dosage, we believe that an estimate of lean body mass may be helpful to shorten the time required to attain a stable dose, particularly in subjects with high BMI values that may be due to increased muscular mass, such as in athletes, or to excessive accumulation of adipose tissue, such as in obese subjects.

Acknowledgments

Received July 6, 2004. Accepted September 21, 2004.

Address all correspondence and requests for reprints to: Ferruccio Santini, Department of Endocrinology, University of Pisa, 56124, Pisa, Italy. E-mail: fsantini@endoc.med.unipi.it.

This work was supported by Ministero dell'Istruzione, dell'-Università e della Ricerca Scientifica, programmi di ricerca cofinanziati 2002 "Obesity: Phenotype characterization and relationship with pathogenesis"; Centro di Eccellenza AmbiSEN "Effects of environmental chemical agents on the endocrine and nervous systems"; Ministero della Salute, programma speciale di sperimentazione 2000 "Strategia multidisciplinare per la prevenzione e la cura dell'obesità e dei disturbi del comportamento alimentare."

References

1. **Roti E, Minelli R, Gardini E, Braverman LE** 1993 The use and misuse of thyroid hormone. Endocr Rev 14:401–423
2. **Mandel SJ, Brent GA, Larsen PR** 1993 Levothyroxine therapy in patients with thyroid disease. Ann Intern Med 119:492–502
3. **Toft AD** 1994 Thyroxine therapy. N Engl J Med 331:174–180
4. **Woeber KA** 2002 Levothyroxine therapy and serum free thyroxine and free triiodothyronine concentrations. J Endocrinol Invest 25:106–109
5. **Pujol P, Daures JP, Nsakala N, Baldet L, Bringer J, Jaffiol C** 1996 Degree of thyrotropin suppression as a prognostic determinant in differentiated thyroid cancer. J Clin Endocrinol Metab 81:4318–4323
6. **Mazzaferri EL** 1987 Papillary thyroid carcinoma: factors influencing prognosis and current therapy. Semin Oncol 14:315–332
7. **Burmeister LA, Goumaz MO, Mariash CN, Oppenheimer JH** 1992 Levothyroxine dose requirements for thyrotropin suppression in the treatment of differentiated thyroid cancer. J Clin Endocrinol Metab 75:344–350
8. **Hermus AR, Huysmans DA** 1998 Treatment of benign nodular thyroid disease. N Engl J Med 338:1438–1447
9. **Hegedus L, Bonnema SJ, Bennedbaek FN** 2003 Management of simple nodular goiter: current status and future perspectives. Endocr Rev 24:102–132
10. **Bartalena L, Pinchera A** 1994 Effects of thyroxine excess on peripheral organs. Acta Med Austriaca 21:60–65
11. **Sawin CT, Geller A, Wolf PA, Belanger AJ, Baker E, Bacharach P, Wilson PW, Benjamin EJ, D'Agostino RB** 1994 Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. N Engl J Med 331:1249–1252
12. **Uzzan B, Campos J, Cucherat M, Nony P, Boissel JP, Perret GY** 1996 Effects on bone mass of long term treatment with thyroid hormones: a meta-analysis. J Clin Endocrinol Metab 81:4278–4289
13. **Fazio S, Palmieri EA, Lombardi G, Biondi B** 2004 Effects of thyroid hormone on the cardiovascular system. Recent Prog Horm Res 59:31–50
14. **England ML, Hershman JM** 1986 Serum TSH concentration as an aid to monitoring compliance with thyroid hormone therapy in hypothyroidism. Am J Med Sci 292:264–266
15. **Franklyn JA, Black EG, Betteridge J, Sheppard MC** 1994 Comparison of second and third generation methods for measurement of serum thyrotropin in patients with overt hyperthyroidism, patients receiving thyroxine therapy, and those with nonthyroidal illness. J Clin Endocrinol Metab 78:1368–1371
16. **Kaplan MM** 1993 Thyroid hormone therapy. What, when, and how much. Postgrad Med 93:249–252, 255–256, 260–262
17. **Sawin CT, Herman T, Molitch ME, London MH, Kramer SM** 1983 Aging and the thyroid. Decreased requirement for thyroid hormone in older hypothyroid patients. Am J Med 75:206–209
18. **Rosenbaum RL, Barzel US** 1982 Levothyroxine replacement dose for primary hypothyroidism decreases with age. Ann Intern Med 96:53–55
19. **Surks MI, Sievert R** 1995 Drugs and thyroid function. N Engl J Med 333: 1688–1694
20. **Alexander EK, Marqusee E, Lawrence J, Jarolim P, Fisher GA, Larsen PR** 2004 Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. N Engl J Med 351:241–249
21. **Cunningham JJ, Barzel US** 1984 Lean body mass is a predictor of the daily requirement for thyroid hormone in older men and women. J Am Geriatr Soc 32:204–207
22. **Pacini F, Capezzone M, Elisei R, Ceccarelli C, Taddei D, Pinchera A** 2002 Diagnostic 131-iodine whole-body scan may be avoided in thyroid cancer patients who have undetectable stimulated serum Tg levels after initial treatment. J Clin Endocrinol Metab 87:1499–1501
23. **Fish LH, Schwartz HL, Cavanaugh J, Steffes MW, Bantle JP, Oppenheimer JH** 1987 Replacement dose, metabolism, and bioavailability of levothyroxine in the treatment of hypothyroidism. Role of triiodothyronine in pituitary feedback in humans. N Engl J Med 316:764–770
24. **Leonard JL, Koerle J** 2000 Intracellular pathways of iodothyronine metabolism. In: Braverman LE, Utiger RD, eds. Werner, Ingbar's The thyroid. A fundamental and clinical text. Philadelphia: Lippincott Williams, Wilkins; 136–173
25. **Wolf M, Weigert A, Kreymann G** 1996 Body composition and energy expenditure in thyroidectomized patients during short-term hypothyroidism and thyrotropin-suppressive thyroxine therapy. Eur J Endocrinol 134:168–173
26. **Haarbo J, Gotfredsen A, Hassager C, Christiansen C** 1991 Validation of body composition by dual energy X-ray absorptiometry (DEXA). Clin Physiol 11: 331–341
27. **Bracco D, Thiebaud D, Chiolero RL, Landry M, Burckhardt P, Schutz Y** 1996 Segmental body composition assessed by bioelectrical impedance analysis and DEXA in humans. J Appl Physiol 81:2580–2587
28. **Friedman JM, Halaas JL** 1998 Leptin and the regulation of body weight in mammals. Nature 395:763–770
29. **Morgan DJ, Bray KM** 1994 Lean body mass as a predictor of drug dosage. Implications for drug therapy. Clin Pharmacokinet 26:292–307
30. **Santini F, Vitti P, Chiovato L, Ceccarini G, Macchia M, Montanelli L, Gatti G, Rosellini V, Mammoli C, Martino E, Chopra IJ, Safer JD, Braverman LE, Pinchera A** 2003 Role for inner ring deiodination preventing transcutaneous passage of thyroxine. J Clin Endocrinol Metab 88:2825–2830
31. **Salvatore D, Bartha T, Harney JW, Larsen PR** 1996 Molecular biological and biochemical characterization of the human type 2 selenodeiodinase. Endocrinology 137:3308–3315
32. **Wesche MF, Wiersinga WM, Smits NJ** 1998 Lean body mass as a determinant of thyroid size. Clin Endocrinol (Oxf) 48:701–706

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.