Variability of L-Thyroxine Replacement Dose in Elderly Patients With Primary Hypothyroidism

Udaya M. Kabadi, MD
Des Moines and Iowa City, Iowa

Sixty-three elderly patients (aged more than 65 years) who manifested primary hypothyroidism during 4½ years from September 1980 to March 1985 were studied. Patients were divided into two groups depending on the presence or absence of chronic associated disorder at the time of diagnosis. Patients in the sick group were required to consume several medications throughout the study period in addition to L-thyroxine for their total therapeutic management. Subjects in the healthy group required L-thyroxine administration alone for their therapy. Prior to institution of L-thyroxine therapy, serum thyroxine (T_4) was not significantly different in the two groups. However, serum triiodothyronine (T_3) and thyroid-stimulating hormone (TSH) levels were significantly lower and T_3 resin uptake was significantly higher in the sick group compared with the healthy patients ($P < .01$ for all comparisons). Furthermore, these differences in T_3, TSH concentration, and T_3 resin uptake values appeared to persist on achieving euthyroid state. The optimal daily L-thyroxine dose was markedly lower (97 ± 3 μg) in the sick patients compared with the healthy group (144 ± 3 μg) as well as with the younger counterparts reported in the literature (150 ± 8 μg). These findings indicate that the decrease in optimal daily L-thyroxine dosage reported in previous studies is not a universal finding in all elderly hypothyroid patients; the decrease is present only in patients with associated chronic disorders, and hence may be attributed to the presence of an associated chronic disorder or medications consumed for treatment of these disorders rather than old age.

Several recent studies reported that the L-thyroxine dose required for achieving euthyroid state in elderly patients with primary hypothyroidism is significantly smaller than the one recommended for their younger counterparts.[1–3] This reduction in optimal L-thyroxine dosage is attributed to the decreased metabolism of thyroid hormones and altered hypothalamic pituitary thyroid axis reported in elderly subjects by numerous previous studies.[4,5] This effect of aging remains inconclusive, however, in the light of other data that demonstrate that the hypothalamic pituitary thyroid axis as well as thyroid hormone metabolism may not be altered in healthy old subjects.[6–8] Thus, it is possible that the decrease in optimal L-thyroxine dosage observed in elderly patients with primary hypothyroidism may be due to associated illness or several medications that such patients consume rather than just "old age," as not only the presence of chronic disorders but also several drugs are known to alter both the thyroid hormone metabolism and the hypothalamic pituitary thyroid axis even in euthyroid subjects.[4,5] Therefore, 63 elderly patients (aged over 65 years) with primary hypothyroidism were studied from the time of diagnosis until the euthyroid state was achieved with L-thyroxine replacement therapy.

METHODS

Sixty-three patients, 58 men and 5 women aged over 65 years (age range 66 to 89 years) determined to be suffering from primary hypothyroidism at the Veterans Administration Medical Center, Des Moines, Iowa, from September 1980 to March 1985 participated in this study after informed consent was obtained. All patients were am-

Submitted, revised, February 6, 1987.

From the Veterans Administration Medical Center, Des Moines, and the Department of Medicine, University of Iowa College of Medicine, Iowa City, Iowa. Requests for reprints should be addressed to Dr. Udaya M. Kabadi, Endocrine Section, Medical Service, VA Medical Center, 30th & Euclid, Des Moines, IA 50310.

bulatory at the time of diagnosis and were studied as outpatients during visits to an endocrinology clinic.

The diagnosis of primary hypothyroidism was established by the presence of several clinical manifestations and documentation of low thyroxine (T_4), low free T_4 index, and elevated basal thyroid-stimulating hormone (TSH) level. In four patients in whom free T_4 indices were at the lowest limit of the normal range and TSH level was slightly elevated, the diagnosis was further confirmed by the documentation of a low serum free T_4 concentration (<1.0 ng/dL) as assessed by a commercial laboratory (Smith, Kline Laboratories, St. Louis, Missouri) and an exaggerated TSH response (ΔTSH > 25 μU/mL) to intravenous thyrotropin releasing hormone (TRH) administration as observed previously in a young as well as in an elderly population in previous studies.[6,9] Serum levels of antithyroglobulin and antimicrosomal antibodies were determined to define the cause of primary hypothyroidism.

The patients in whom L-thyroxine therapy was to be suppressive following thyroid surgery for cancer or nodule as well as for suppression of goiter were excluded because the suppressive L-thyroxine dose is often higher than the optimal replacement L-thyroxine dosage. Patients with subclinical hypothyroidism as documented by normal T_4 and triiodothyronine (T_3) resin uptake levels and high TSH concentrations were also excluded because they are known to require a smaller daily dose of L-thyroxine to achieve euthyroidism than patients with manifest hypothyroidism.[10]

The patients were divided into two groups regardless of the cause of primary hypothyroidism. One group consisted of patients in whom primary hypothyroidism was the only disorder present. The other group included patients in whom primary hypothyroidism was manifest in the presence of previous associated diseases such as hypertension, atherosclerotic heart disease, diabetes mellitus, chronic obstructive pulmonary disease, cirrhosis of the liver, malignancy, etc. All these disorders were included in the same group because thyroid hormone metabolism and hypothalamic pituitary thyroid axis are known to be altered in the presence of any acute or chronic disorder resulting in altered thyroid hormone concentrations as well as inhibited TSH response to intravenous TRH administration, even though the patients are euthyroid.[5] Most of the patients in this group were also treated with some medication at the time of diagnosis of hypothyroidism and were required to continue the medication for their total therapeutic management throughout the study period.

All patients were started on L-thyroxine replacement therapy, with the initiating dose of 25 μg/d. Patients were examined and evaluated at intervals of two to four weeks in the Endocrinology Clinic. L-Thyroxine dosage was increased by 25 μg every two to four weeks in the absence of untoward symptoms, ie, chest pain, tachycardia, or exertional dyspnea, until a dose of 100 μg was reached or patients were apparently clinically euthyroid. In patients who reported untoward symptoms during the follow-up visit, the L-thyroxine dose was reduced to the previous dose, and the previous dose was continued for four weeks and then increased. In all patients, serum levels of T_4, T_3, T_3 resin uptake, and TSH were determined during each follow-up visit, and the dose of L-thyroxine was adjusted until basal TSH level normalized (<8μU/mL). At this juncture, serum TSH concentration was determined after an overnight fast and again at 30 and 60 minutes after an intravenous bolus administration of 500 μg TRH (protirelin), and L-thyroxine dosing was further adjusted depending on the TSH response to TRH administration as described previously.[3,9] Serum T_4, T_3 resin uptake, T_3, and TSH concentrations were determined after the L-thyroxine dose was considered optimal as established by normal TSH response (ΔTSH) to TRH administration (peak minus basal TSH level = 5 to 25 μU/mL) on two successive clinic visits at intervals of four to six weeks.

Serum T_4, T_3, and TSH were assessed by previously well-established radioimmunoassay techniques.[11–13] Antimicrosomal and antithyroglobulin antibodies as well as serum T_3 resin uptake were determined by using commercial kits (Zeus, Inc, Raritan, NJ; and Nuclear Medical, Inc, Irving, Texas, respectively). Statistical analyses were performed by Student's *t* test. All data are reported as mean ± standard error of mean.

RESULTS

Of 63 patients, 36 belonged to the group that also manifested a chronic disorder at the onset of hypothyroidism (group 1). The chronic disorders present in patients belonging to this group are displayed in Table 1 and the medications consumed by these patients are displayed in Table 2. The remaining 27 patients manifested primary hypothyroidism as the only disorder (group 2). The body weight for the sick group was significantly lower ($P < .05$) compared with the healthy group (Table 3).

Fifteen patients in the sick group and 20 patients in the healthy group 2 were determined to have Hashimoto's or autoimmune thyroiditis as defined by antimicrosomal or antithyroglobulin antibody titers of greater than 1:100. Ten patients in group 1 and seven patients in the healthy group may be classified as idiopathic, as the antithyroid antibodies were negative. However, autoimmune causes may be possible in this group as well, since a recent study reported cytologic abnormalities consistent with Hashimoto's thyroiditis in absence of significant titers of antithyroglobulin or antimicrosomal antibodies in their sera.[14] The remaining 11 patients in the sick group were hypothyroid as a result of neck surgery or radiation therapy to

TABLE 1. CHRONIC DISORDERS PRESENT IN HYPOTHYROID PATIENTS*

Atherosclerotic heart disease
Coronary artery disease
Chronic congestive heart failure
Cerebrovascular disease
Cirrhosis of liver
Chronic alcoholism
Hypertension
Chronic renal failure
Diabetes mellitus
Malnutrition
Chronic obstructive pulmonary disease
Sideroblastic anemia
Metastatic cancer
Rheumatoid arthritis
Parkinsonism, depression

** Many patients had more than one disorder during the study period*

TABLE 2. MEDICATIONS CONSUMED BY HYPOTHYROID PATIENTS*

Diuretics including furosemide, thiazides, spironolactone
Isosorbide dinitrate
Beta-blockers
Calcium channel blockers
Digoxin
α-Methyldopa
Theophylline
Nonsteroidal antiinflammatory agents including aspirin
Tricyclic antidepressants
Glucocorticoid
L-Dopa
Antacid

** Many patients consumed more than one medication during the study period*

the neck for cancer of the larynx or tongue or for Hodgkin's disease.

Untoward symptoms, ie, chest pain, tachycardia, dyspnea, etc, were reported during L-thyroxine replacement therapy by only one patient, who had a history of coronary artery disease. In this case, optimal L-thyroxine replacement was achieved by concurrent therapy with nifedipine. None of the other patients, including five patients with a history of coronary artery disease, experienced untoward symptoms.

Prior to L-thyroxine replacement therapy, serum T_4 levels were not significantly different in either of the groups of elderly hypothyroid patients. Serum T_3 and TSH levels were markedly lower, however, and T_3 resin uptake was significantly higher in elderly hypothyroid patients with other associated disorders (group 1) when compared with those concentrations in patients with primary hypothyroidism as the only manifest disorder (group 2) (Table 3). On achieving and maintaining an euthyroid state with the optimal L-thyroxine dose, serum T_4 and T_3 concentrations, though within normal limits for both groups, were significantly lower in hypothyroid patients with other associated disorders (group 1) compared with those concentrations of the group with hypothyroidism as the only manifest disorder (group 2) (Table 4). Furthermore, T_3 resin uptake values continued to be significantly higher in the sick hypothyroid group (group 1) compared with those of the healthy group (group 2). Finally, basal TSH levels were not significantly different when compared in both groups. However, TSH response (ΔTSH) to intravenous TRH administration, though within normal range (5 to 25 μU/mL), was significantly lower in sick hypothyroid patients compared with response of the healthy group. These differences in thyroid hormone levels appeared independent of the cause of hypothyroidism.

The optimal daily dose of L-thyroxine as reflected by normalization of both the basal TSH level and TSH response to intravenous TRH administration was markedly lower ($P < .01$) in the group of hypothyroid elderly patients with associated disorders (75 to 125 μg/d) than in the other group with primary hypothyroidism as the only manifest disease (125 to 175 μg/d) (Table 4). Furthermore, even if the L-thyroxine dose was estimated as microgram per kilogram of body weight, the mean dose was still significantly smaller ($P < .05$) in the sick group (1.67 ± 0.11 μg/kg) than in the healthy group (2.15 ± 0.13 μg/kg).

DISCUSSION

This study documents that prior to institution of L-thyroxine therapy, serum T_3 levels were significantly lower and T_3 resin uptake was significantly higher in sick hypothyroid patients than in patients without associated chronic disorders, and these differences appeared to persist after achieving euthyroid state. Moreover, during euthyroid state both serum T_4 and T_3 concentrations, although within normal range, were markedly lower in sick hypothyroid patients than in the healthy group. These findings may represent altered thyroid hormone metabolism existent in elderly sick hypothyroid patients, and may be consistent with the previous studies that reported lowering of serum T_3 or T_4 levels and increased T_3 resin uptake values in sick euthyroid subjects of any age, young or old,[6,7,15] as well as several other "euthyroid sick" states[5,16–20] and drug-induced alterations in thyroid functions.[5] Finally, lower basal TSH level noted prior to L-thyroxine replacement therapy and a significantly smaller TSH response (ΔTSH) to intravenous TRH administration on achieving euthyroidism in elderly sick hypothyroid subjects may be indicative of a subtle dysfunction of hypothalmic-pituitary-thyroid axis reported previously in euthyroid sick states.[5,20] Alternatively, a higher free T_4 con-

TABLE 3. SERUM T_4, T_3, T_3 RESIN UPTAKE (T_3RU), AND BASAL TSH CONCENTRATIONS IN TWO GROUPS OF ELDERLY HYPOTHYROID PATIENTS (mean ± standard error of mean)

Patients by Group*	Age years	Body Weight kg	T_4 μg/dL	T_3RU %	T_3 ng/dL	TSH μU/mL
1. Sick	72 ± 6	58 ± 3**	3.5 ± 0.2	29.2 ± 0.8**	82 ± 5**	47 ± 6**
2. Healthy	71 ± 8	67 ± 4	4.1 ± 0.3 (5.5–11.5)***	25.1 ± 0.4 (25–35)	108 ± 6 (110–190)	71 ± 6 (<8)

* *Divided according to presence (sick) or absence (healthy) of associated disorders*
** *Significantly different from group 2, P < .01*
*** *Normal range in endocrine laboratory of VA Medical Center is shown in parentheses*

TABLE 4. OPTIMAL L-THYROXINE DOSAGE, SERUM T_4, T_3, T_3RU, AND BASAL TSH CONCENTRATIONS, AS WELL AS TSH RESPONSE (ΔTSH) TO INTRAVENOUS TRH ADMINISTRATION, ON ACHIEVING EUTHYROID STATE IN TWO GROUPS OF ELDERLY PATIENTS WITH PRIMARY HYPOTHYROIDISM (mean ± standard error of mean)

Patients by Group*	Total L-Thyroxine Dose μg	L-Thyroxine Dose μg/kg	T_4 μg/dL	T_3RU %	T_3 ng/dL	ΔTSH μU/mL	ΔTSH μU/mL
1. Sick	97 ± 3**	1.67 ± 0.11**	8.2 ± 0.3**	32.2 ± 0.6**	116 ± 4**	3.6 ± 0.4	10 ± 2**
2. Healthy	144 ± 3	2.15 ± 0.13	9.5 ± 0.3	29.1 ± 0.4	136 ± 4	3.0 ± 0.3	18 ± 3

* *Groups are divided according to Table 2*
** *Significantly different from group 2, P < .01*

centration may have been responsible for the differences in TSH regulation observed between the sick and the healthy hypothyroid study groups. A great overlap in free T_4 values reported by several studies in euthyroid sick states,[21–23] however, may render this explanation less credence.

This study also demonstrates that the optimal L-thyroxine dosage required for achieving and maintaining euthyroid state in elderly patients with primary hypothyroidism is not always decreased. This finding is in contrast to the earlier studies,[1-3] which reported lower optimal L-thyroxine dosage in elderly patients with primary hypothyroidism. These studies, however, failed to indicate the presence or absence of associated chronic disorders in their patients, an important difference from this study in which the lowering of L-thyroxine dose was observed only in sick hypothyroid elderly patients who manifested a chronic disease and were on certain medications prior to onset of hypothyroidism and not in healthy patients with hypothyroidism as the only manifest disorder. Furthermore, in some of these studies,[1,2] normalization of basal TSH level was used as the end point of L-thyroxine replacement therapy. In this study the normalization of both the basal TSH level as well as TSH response to intravenous TRH administration were used as the indices of optimal L-thyroxine dosage, as normal TSH response to intravenous TRH administration was recently demonstrated to be the best index of optimal L-thyroxine replacement therapy.[9] Finally, if the blunted TSH response to intravenous TRH administration as observed in euthyroid sick states[5] were chosen as the end point of L-thyroxine replacement therapy in hypothyroid sick patients, the optimal L-thyroxine dosage may have been still closer to the dosage used in healthy elderly hypothyroid patients as well as in their younger counterparts as described in the literature.[24,25] The reason for the lower optimal L-thyroxine dosage required by elderly sick hypothyroid patients is unclear. It may be attributed to altered thyroid hormone metabolism or inhibited binding of thyroid hormones to their binding protein documented in euthyroid sick syndrome or induced by ingestion of certain drugs and thus resulting in the previously documented relative elevations of free T_4 concentrations and T_3 resin uptake values.[26–30]

It is also apparent from this study that use of an extremely small initial dose of L-thyroxine (25 μg/d) and gradual increase in the dosage by 25 μg every four weeks prevent the occurrence of untoward manifestations in most elderly patients. Similar data were recently reported[3]; therefore, similar protocol of L-thyroxine replacement therapy is often recommended in elderly patients.

In conclusion, this study clearly demonstrates that the reduced dosage of L-thyroxine is required only in elderly patients with primary hypothyroidism who manifest a chronic associated disorder and not in all elderly hypothyroid subjects as reported previously.[1–3] Furthermore, this decrease in L-thyroxine dosage may be mainly a reflection of an associated chronic disorder rather than of old age. However, the consumption of certain drugs may have contributed to the decrease in L-thyroxine dosage as well.

Acknowledgment

This work was supported by research grants from the Veterans Administration, Washington, DC.

References

1. Rosenbaum RL, Barzel US: Clinical hypothyroidism in the elderly—A preventable disorder? J Am Geriatr Soc 1981; 29:221–223
2. Rosenbaum R, Barzel US: Levothyroxine replacement dose for primary hypothyroidism decreases with age. Ann Intern Med 1982; 96:53–55
3. Davis FB, LaMantia RS, Spaulding SW, et al: Estimation of a physiologic replacement dose of levothyroxine in elderly patients with hypothyroidism. Arch Intern Med 1984; 144:1752–1754
4. Gregerman RI, Gaffney GW, Shock NW: Thyroxine turnover in euthyroid man with special reference to changes with age. J Clin Invest 1962; 41:2065–2074
5. Wartofsky L, Burman KD: Alterations in thyroid function in patients with systemic illness: The "euthyroid sick syndrome." Endocr Rev 1982; 3:164–217
6. Olsen T, Laurbert P, Jorgen W: Low serum triiodothyronine and high serum reverse triiodothyronine in old age: An effect of disease, not age. J Clin Endocrinol Metab 1978; 47:1111–1115
7. Havard CWH: The thyroid and aging. Clin Endocrinol Metab 1981; 10:163–178
8. Kabadi UM, Rosman P: Thyroid hormone concentrations and hypothalamic pituitary thyroid axis are not affected by "aging." In Proceedings of the Annual Meeting of American Geriatrics Society. New York, American Geriatrics Society, 1985, p 45
9. Kabadi UM: Normal thyrotropin response to IV thyrotrophin releasing hormone administration: The best index of optimal L-thyroxine therapy in primary hypothyroidism. Postgrad Med J 1985; 61:685–688
10. Cooper DS, Halpern R, Wood LC, et al: L-Thyroxine therapy in subclinical hypothyroidism: A double-blind, placebo-controlled trial. Ann Intern Med 1984; 101:18–24
11. Premachandra BN, Ibrahim II: A simple and rapid thyroxine radioimmunosassay (T_4-RIA) in unextracted human serum: A comparison of T_4-RIA and T_4 displacement assay (T_4(D) in normal and pathologic sera. Clin Chim Acta 1976; 70:43–60
12. Premachandra BN: A simple and rapid radioimmunoassay of triiodothyronine in unextracted serum. J Nucl Med 1976; 17:411–416
13. Dimond RC, Rosen SW: Chromatographic differences between circulating and pituitary thyrotropins. J Clin Endocrinol Metab 1974; 39:316–325
14. Baker BA, Hossein G, Markowitz H: Correlation of thyroid antibodies and cytologic features in suspected autoimmune thyroid disease. Am J Med 1983; 74:941–944
15. Kabadi UM, Premachandra BN: Low triiodothyronine and raised reverse triiodothyronine levels in patients over fifty years of age who have type II diabetes mellitus: Influence of metabolic control, not age. J Am Geriatr Soc 1984; 32:375–379
16. Burger A, Nicod P, Suter P, et al: Reduced active thyroid hormone levels in acute illness. Lancet 1976; 1:653–655
17. Chopra IJ, Chopra U, Smith SR, et al: Reciprocal changes in serum concentrations of 3,3′,5′-triiodothyronine (reverse T_3) and 3,5,3′-triiodothyronine (T_3) in systemic illnesses. J Clin Endocrinol Metab 1975; 41:1043–1049
18. Kabadi UM, Premachandra BN, Maayan M: Low serum 3,5,3′-triiodothyrone (T_3) and raised 3,3′,5′-triiodothyronine (reverse T_3 or RT_3) in diabetes mellitus: Normalization on improvement in hyperglycemia. Acta Diabetol Lat 1982; 19:233–242
19. Kabadi UM, Premachandra BN: Serum T_3 and reverse T_3 levels in hepatic cirrhosis: Relation to hepatocellular damage and normalization on improvement in liver dysfunction. Am J Gastroenterol 1983; 78:750–755
20. Kabadi UM: Altered thyrotropin secretion in uncontrolled type II diabetes mellitus and its normaliztion on attainment of eumetabolic state. J Clin Endocrinol Metab 1984; 59:521–525
21. Green WL, Felicetta JV, Ryan F, Kenny MA: The proper use of the triiodothyronine resin uptake and free thyroxine index, abstract. In 61st Annual Meeting of The Endocrine Society program. Anaheim, Calif, The Endocrine Society, 1979, p 298
22. Chopra IJ, Van Herle AJ, Chua Teco GN, Nguyen AH: Serum free thyroxine in thyroidal and nonthyroidal illnesses: A comparison of measurements by radioimmunoassay, equilibrium dialysis, and free thyroxine index. J Clin Endocrinol Metab 1980; 51:135–143
23. Chopra IJ, Solomon DH, Hepner GS, Morgenstein AA: Misleadingly low free thyroxine index and usefulness of reverse triiodothyronine measurement in nonthyroidal illnesses. Ann Intern Med 1979; 90: 905–912
24. Cotton GE, Gorman CA, Mayberry WE: Suppression of thyrotropin (h-TSH) in serums of patients with myxedema of varying etiology treated with thyroid hormones. N Engl J Med 1971; 285:529–533
25. Stock JM, Surks MI, Oppenheimer JH: Replacement dosage of L-thyroxine in hypothyroidism: A reevaluation. N Engl J Med 1974; 290:529–533
26. Kaptein EM, MacIntyre SS, Weiner JM, et al: Free thyroxine estimates in nonthyroidal illness: Comparison of eight months. J Clin Endocrinol Metab 1981; 52:1073–1077
27. Woeber KA, Maddux BA: Thyroid hormone binding in nonthyroidal illness. Metabolism 1981; 30:412–416
28. Chopra IJ, Chua Teco GN, Nguyen AH, Solomon DH: In search of an inhibitor of thyroid hormone binding to serum proteins in enonthyroid illnesses. J Clin Endocrinol Metab 1979; 49:63–69
29. Oppenheimer JH, Schwartz HL, Mariash CN, Kaiser FE: Evidence for a factor in the sera of patients with nonthyroidal disease which inhibits iodothyronine binding by solid matrices, serum proteins, and rat hepatocytes. J Clin Endocrinol Metab 1982; 54:757–766
30. Chopra IJ, Solomon DH, Chua Teco GN, Eisenberg JB: An inhibitor of the binding of thyroid hormones to serum proteins is present in extrathyroidal tissues. Science 1982; 215:407–409