THYROID
Volume 6, Number 3, 1996
Mary Ann Liebert, Inc.

Effect of L-Thyroxine Administration on Antithyroid Antibody Levels, Lipid Profile, and Thyroid Volume in Patients with Hashimoto's Thyroiditis

JOÃO H. ROMALDINI, MARCOS M. BIANCALANA, DULCE I. FIGUEIREDO, CHADY S. FARAH, and PAULO C. MATHIAS

ABSTRACT

The changes in the serum thyroid autoantibodies, antithyroglobulin (TgAb) and antithyroid-peroxidase (TPOAb), lipid profile, and thyroid volume following L-thyroxine (L-T_4) therapy is still a controversial matter. We studied 23 patients with goiter due to Hashimoto's thyroiditis; 10 had clinical hypothyroidism (CH) and 13 had subclinical hypothyroidism (SH). Both groups received L-T_4 (2.0 to 2.5 μg/kg/day) for a median period of 6 months. Serum concentration of TgAb (normal value: <200 mUI/mL) and TPOAb (normal value: <150 mUI/mL) were measured by a sensitive IRMA using ^{125}I protein-A. Thyroid volume was determined by ultrasound (normal value: 8–14 mL). At the end of the observation period the median serum TSH concentration decreased significantly in both groups (42.9 to 0.55 in CH and 2.4 to 0.74 mU/L in SH patients) and serum FT_4I levels increased only in the CH group (0.87 to 2.1; $p < 0.05$). Serum TgAb concentration did not change in SH patients (72 to 218 mUI/mL) but declined in CH patients (364.5 to 75 mUI/mL; $p < 0.05$). TPOAb levels also fell in the CH group (871 to 194 mUI/mL; $p < 0.05$) and no significant change was noted in SH patients (260 to 116 mUI/mL). Further, a significant correlation was obtained between TSH and either TPOAb concentration ($r_s = 0.569$, $p < 0.01$) or thyroid volume ($r_s = 0.488$, $p < 0.05$) in the CH group but not in SH patients ($r_s = 0.232$, NS). LDL-cholesterol was higher in the CH (159.4 mg/dL) compared with the SH group (116 mg/dL). Moreover, only in the CH patients was there a significant fall in total cholesterol (224.5 to 165.5 mg/dL, $p < 0.05$) and in LDL-cholesterol (159.4 to 104.3 mg/dL, $p < 0.05$) values. The thyroid volume decreased in all patients with CH and in 77% (10/13) of SH patients and a significant median in the thyroid volume decrease was found (39.7% of initial volume in the CH group and 80.9% in SH patients; $p < 0.01$). The influence of L-T_4 on both thyroid autoantibody levels and thyroid volume might be explained by reduction of antigenic substance through a decreased stimulation of thyroid tissue by circulating TSH as was seen in CH but not in SH patients. The benefits of the administration of L-T_4 replacement therapy in SH patients due to Hashimoto's thyroiditis remain to be clarified.

INTRODUCTION

THE CHANGES IN THE SERUM THYROID AUTOANTIBODIES, antithyroglobulin (TgAb), and antithyroperoxidase (TPOAb), lipid profile, and thyroid volume following L-thyroxine (L-T_4) therapy is still a controversial matter (1–4). A decrease of TgAb and TPOAb levels in adult patients with Hashimoto's thyroiditis treated with thyroid hormone was observed by some authors (4–8) but not by others (9–11), and the assay methodologies used could explain these discrepancies. It is well known that total cholesterol, triglycerides, and LDL-cholesterol (LDL-C) are elevated in the serum of patients with hypothyroidism and their improvement after hormonal replacement (12–19). Regarding the decrease of thyroid size, as far as we know few studies were performed, and among these Hegedus et al. (1) found a significant reduction of goiter determined sonographically in patients with Hashimoto's thyroiditis without any correlation with thyroid antibody levels. In the present study, we evaluated the influence of L-T_4 administration on the thyroid volume using a high resolution ultrasound and we studied its relationship with serum

Department of Endocrinology, Hospital do Servidor Publico Estadual-IAMSPE, C.P. 8570-01000, São Paulo, SP, Brazil.

TgAb and TPOAb changes and lipid profile in goitrous Hashimoto's patients with clinical hypothyroidism (CH) and subclinical hypothyroidism (SH).

PATIENTS AND METHODS

Patients

Twenty-three patients (21 women and two men) with firm palpable goiter were studied. The diagnosis of Hashimoto's thyroiditis was based on clinical criteria and confirmed by a finding of elevated TgAb and or TPOAb levels, and the patients were separated into two groups. Ten patients with CH, nine women and one man, median age 40 years (range: 17–70 years). All CH patients had high basal TSH levels and low FT_4I. The remaining 13 patients (12 women and one men), median age 43 years (range: 8–72 years) with SH defined as clinically euthyroid, normal T_4 and FT_4I values but borderline raised serum TSH concentration (three patients) or exaggerated response of TSH to TRH in 10 patients with median peak of 30.1 mU/mL (25–48.6 mU/mL). All patients were in good health and did not take drugs that could interfere with lipoprotein metabolism.

Both groups were treated for a median period of 6 months with L-T_4 with doses of 2.0 to 2.5 μg/kg/day. The protocol of this study was approved by the ethics committee of the hospital.

Methods

Serum T_4 and T_3 concentrations and T_3 uptake values were measured with commercially available kits from Diagnostic Products Corporation (Los Angeles, CA). Serum FT_4I was calculated from T_4 concentration and uptake value. Normal ranges were 4.5 to 12.5 μg/dL for T_4, 80 to 210 ng/dL for T_3, and 1.3 to 4.5 for FT_4I. Serum TSH concentrations were measured by an immunoradiometric assay (IRMA) using a Serono Diagnostic kit (Norwell, MA), and the normal range was 0.35 to 4.5 mU/mL. Interassay and intraassay coefficients of variation for each assay were as follows: 4.8 and 3.5% for T_4, 6.1 and 3.8% for T_3, 6.7 and 4.5% for T_3 uptake, and 4.6 and 3.2% for TSH, respectively (20). Serum concentrations of TgAb and TPOAb were measured by sensitive IRMA method (21) using ^{125}I protein-A with a sensitivity of 1.2 mIU/mL (Ciba-Corning Diagnostic, MA). The normal values were less than 200 mIU/mL for TgAb and less than 150 mIU/mL for TPOAb. Interassay and intraassay coefficient of variation were 8.2 and 7.2% for TgAb and 6.2 and 4.8% for TPOAb, respectively. Total cholesterol, triglycerides, and HDL-cholesterol (HDL-C) were measured by enzymatic method (22) using kits from Boehringer Mannheim (GmbH Diagnostic, Mannheirm, Germany). The normal values were total cholesterol, less than 200 mg/dL; triglycerides, 40 to 200 mg/dL; and HDL, 30 to 85 mg/dL. Very low-density lipoprotein (VLDL-C) was calculated from triglyceride values by the formula triglycerides/5, and normal values were less than 30 mg/dL. LDL-C was calculated by the formula LDL-C = total cholesterol − (HDL-C + VLDL-C), and the normal values were less than 130 mg/dL. All samples of fasting serum from each individual patient were collected before treatment and each two months after L-T_4 therapy. The serum samples were in all instances stored at −20°C and analyzed in the same assays.

Thyroid size was determined by ultrasound, before and at the end of observation on L-T_4 using a Toshiba SAL 240 apparatus with a transductor of 7.5 MHz. The total thyroid volume gland was calculated from the sum of the partial volumes: $V = V$ right lobe + V left lobe + V isthmus. The volume of every part was calculated by $V_0 = p/6 \times$ (length × width × thickness). Normal values were 8 to 14 mL.

Statistical analyses were performed by Wilcoxon test, Mann–Whitney test, Spearman rank correlation coefficient, and analysis of variance. A value of $p < 0.05$ was considered significant.

TABLE 1. CHANGES IN THYROID HORMONES, ANTITHYROID ANTIBODIES, AND THYROID VOLUME IN PATIENTS WITH HASHIMOTO'S THYROIDITIS FOLLOWING HORMONAL REPLACEMENT WITH L-THYROXINE[a]

	Clinical hypothyroidism (n=10)		*Subclinical hypothyroidism (n=13)*	
	Before	*After*	*Before*	*After*
Thyroid volume (mL)	25.9 (14–87)	8.5* (6–58.3)	16.2 (6.5–65.8)	11.7* (3.1–44.5)
TPOAb (mUI/mL)	871 (240–9000)	194* (34–4000)	260 (22–2830)	116 (9–1194)
TgAb (mUI/mL)	364 (28–1563)	75* (18–1094)	72 (46–2088)	218 (36–1359)
TSH (mU/mL)	42.9 (18–106.4)	0.55* (0.06–9.2)	2.4 (1.1–19)	0.74* (0.18–3.2)
FT_4I	0.87 (0.2–1.3)	2.1* (1.5–4.5)	1.73 (1.9–2.9)	2.27 (1.1–3.7)

[a]The values are expressed in median (range).
*$p < 0.05$.

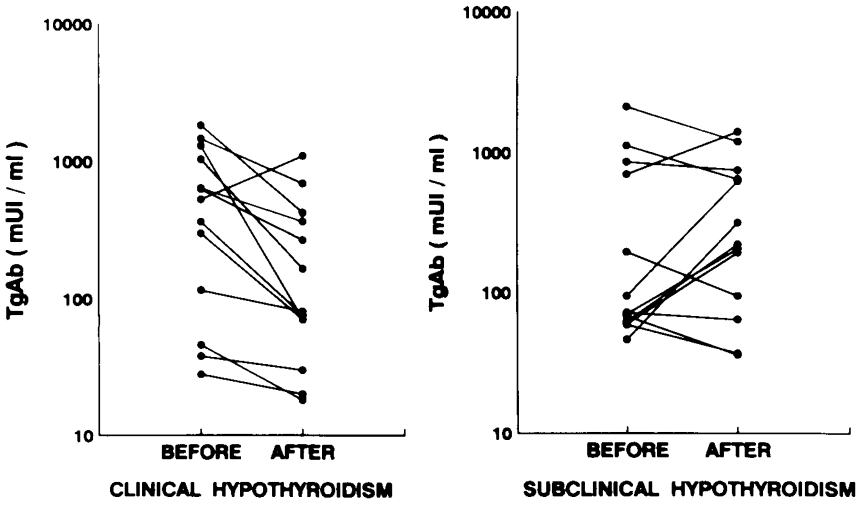

FIG. 1. Serum TgAb concentrations in individual patients with clinical and subclinical hypothyroidism due to Hashimoto's thyroiditis before and after 6 months of L-T_4 replacement therapy.

RESULTS

At the end of observation period (Table 1) the serum FT_4I levels increased significantly only in the CH group and the serum TSH levels decreased significantly in both groups.

Serum TgAb concentration was similar in SH and in CH patients. Serum TPOAb concentration in the CH group was significantly higher compared to the value found in SH patients. Treatment with L-T_4 as shown in Figure 1 was associated with a significant decline of serum TgAb concentration in CH but did not in SH patients. Serum TPOAb values also decreased in CH patients (Fig. 2) and did not significantly change in SH patients.

Regarding the lipid profile, LDL-C levels in CH patients were significantly higher compared to the value found in SH patients before pretreatment with L-T_4. Other serum lipid concentrations were similar in both groups as shown in Table 2. During L-T_4 therapy both the total cholesterol and LDL-C values did not change significantly in SH, but they fell in CH patients. No significant changes were observed in serum concentrations of HDL-C, VLDL-C, and triglycerides in both groups.

A decrease in the thyroid gland volume by ultrasound determination with respect to pretreatment value was observed in both groups (Fig. 3). A significant ($p < 0.01$) decrease related to initial volume was found in the CH group (80.9%) in comparison with SH patients (38.7%). A median significant decrease of 67% in the thyroid volume was noted in the CH group and only 28% in SH patients (Table 1). All patients with CH showed a decrease of thyroid volume, and this was found in nine (69.2%) out of 13 of the SH patients also. In this group two (15.3%) patients did not change the thyroid volume and we noted an increase after L-T_4 therapy in another two (15.3%) patients (Fig. 3).

In patients of the CH group, we have also observed a significant correlation between TSH concentration and ei-

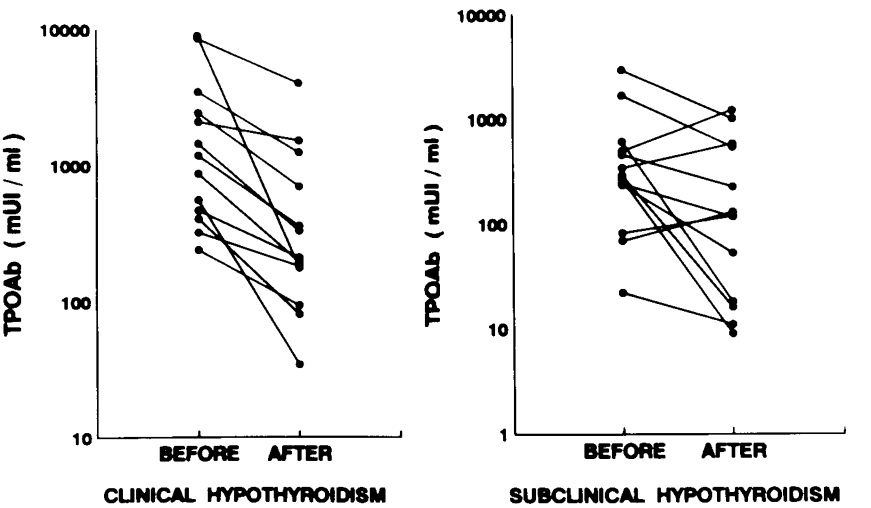

FIG. 2. Serum TPOAb concentrations in individual patients with clinical and subclinical hypothyroidism due to Hashimoto's thyroiditis before and after 6 months of L-T_4 replacement therapy.

TABLE 2. LIPID PROFILE CHANGES IN PATIENTS WITH HASHIMOTO'S THYROIDITIS FOLLOWING HORMONAL REPLACEMENT WITH L-THYROXINE

	Clinical hypothyroidism (n = *10*)		*Subclinical hypothyroidism* (n = *13*)	
	Before	*After*	*Before*	*After*
Total cholesterol (mg/dL)	224.5 (133–428)	165.5* (124–201)	200 (120–286)	176 (120–243)
LDL-C (mg/dL)	159.4 (78–370)	104.3* (73–138)	116 (72–217)	107.2 (72–163)
HDL-C (mg/dL)	35 (25–66)	35 (26–64)	38 (27–61)	36 (27–52)
VLDL-C (mg/dL)	29.7 (9–42)	23.7 (7–37.5)	25.9 (13–60)	24.6 (12–37)
Triglycerides (mg/dL)	148.5 (47–210)	118.5 (33–188)	127 (67–300)	123 (71–187)

[a]The values are expressed in median (range).
*$p < 0.05$.

ther TPOAb ($r_s = 0.569$, $p < 0.01$; $n = 20$) or thyroid volume ($r_s = 0.488$, $p < 0.05$; $n = 20$) levels but not with TgAb concentration ($r_s = 0.232$, NS; $n = 20$). In contrast, no correlation was observed in SH patients using these parameters. Furthermore, no significant correlation was observed among lipid profile and antithyroid antibody levels, thyroid hormone values, TSH concentration, and thyroid volume.

DISCUSSION

The present study shows that administration of L-T_4 was associated with a significant reduction in serum TgAb and TPOAb concentration in patients with CH due to Hashimoto's thyroiditis. This cannot be accounted for as a spontaneous variation, since no significant decrease in serum TgAb and TPOAb levels was observed in SH patients with Hashimoto's thyroiditis. These findings are in agreement with some (5–8,11) but not with other studies (1,4,9,10). These discrepancies may be partly explained by methodologic differences in the determination of serum TgAb and TPOAb levels. Two-fold and even four-fold dilution are commonly employed in complement fixation and passive hemagglutination methods (4), and under these conditions modifications of antibody levels up to 50% or more may not be detected (8). In this respect, as recently reported by Mariotti et al. (23), the use of precise and quantitative radioassay methods, such as the one employed in the present study, provides a clear advantage due to improvement in the sensitivity and precision of the IRMA assay (21,24,25). The influence of L-T_4 on the thyroid antibody levels fall can be attributed to several mechanisms. The recovery of euthyroidism (5,6,20,26,27) may be the reason for our result. It is believed that an excessive amount of thyroid antigens is exposed in the CH group, as influenced by higher TSH concentration. As reviewed by Harbour (28), both TSH and T_4 may be part of the neuroendocrine immune axis that directly stimulates the lymphocytes responsible for the production of thyroid autoantibodies, and thus thyroid status can modulate thyroid autoimmunity expression (29). A more likely explanation is that L-T_4 might reduce the antigenic substance in the thyroid gland through a decreased stimulation of thyroid tissue by circulating TSH (30), as was seen by decreasing TSH and increasing FT_4I values in CH patients with goitrous Hashimoto's thyroiditis but not in SH patients. In addition, a significant correlation was also found between TSH and TPOAb concentrations only in the CH group. Thyroid hormones affect the serum LDL-C level at several loci (19). Lowered fractional clearance of LDL particles by the liver is the major cause of the hypercholesterolemia in hypothyroid patients. Moreover, studies in hypothyroid rats showed reduced expression of hepatic LDL receptors (13). Although a mild decrease of total cholesterol and LDL-C

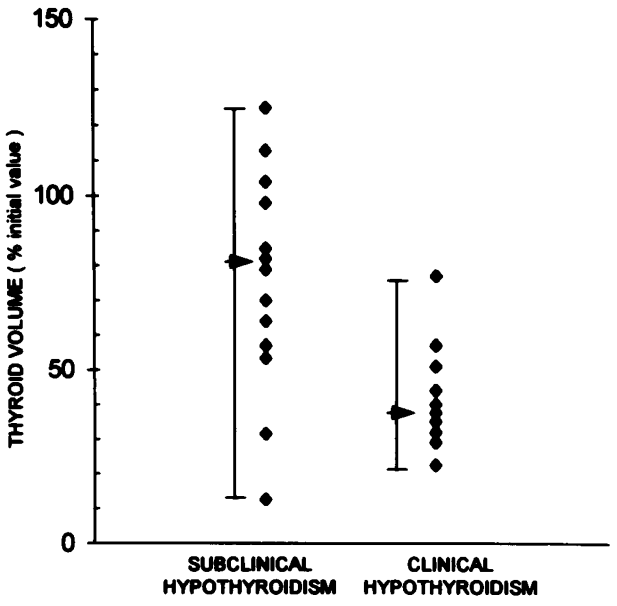

FIG. 3. Median (range) of changes in the thyroid volume values measured by ultrasound in patients with clinical and subclinical hypothyroidism due to Hashimoto's thyroiditis after 6 months of L-T_4 replacement therapy.

was noted in SH patients, a significant decrease was found in the CH group. These results are in agreement with previous reports (2,17,18,31,32), but are in sharp contrast with other studies that showed significant improvement of lipid profile after L-T_4 therapy in SH patients (14–17,33). Our findings of a significant decrease in thyroid volume after L-T_4 administration confirmed the results of Hegedus et al. (1). The further enlargement of the thyroid gland observed in some patients could be ascribed to the presence of thyroid growth-promoting antibodies (34). However, in a recent report Vitti et al. (35) did not detect such antibody, arguing against a direct role of it in the development of goiter. In CH patients we noted a significantly greater decrease in thyroid volume than in SH patients, suggesting that the circulating TSH might be the main factor responsible for the goiter increase. The observation of a significant correlation of TSH and thyroid volume values in CH patients may support this hypothesis. Finally, a distinct effect of L-T_4 therapy could be observed in serum TgAb and TPOAb concentration, lipid profile, and thyroid volume in CH patients. On the other hand, it is not yet clear whether the metabolic change observed in SH patients indicates that L-T_4 administration should be given. Staub et al. (36) recommended that the hormonal replacement should take place when an elevated TSH value (higher than 12 mU/mL) is found. The benefits and long-term side effects of L-T_4 therapy in SH patients with Hashimoto's thyroiditis remain to be clarified.

ACKNOWLEDGMENTS

This work was supported by a grant of FAPESP. Presented in part at the Sixty-Seventh Annual Meeting of American Thyroid Association, November 10–14, 1993, Tampa, Florida (abstract 45). We are grateful to Carmela Ambrico, Maria C. Rodrigues, and Ester L. Ribeiro for their technical assistance.

REFERENCES

1. Hegedus L, Hansen JM, Feldt-Rasmussen U, Hansen BM, Madesen MH 1991 Influence of thyroxine treatment on thyroid size and antithyroid peroxidase antibodies in Hashimoto's thyroiditis. Clin Endocrinol 35:235–244.
2. Bogner U, Arntz HR, Peters H, Schleusener H 1993 Subclinical hypothyroidism and hyperlipoproteineaemia: Indiscriminate L-thyroxine treatment not justified. Acta Endocrinol 128:202–206.
3. Miura S, Itaka M, Yoshimura H, Kitahama S, Fukasawa N, Kawakami Y, Sakurai S, Urabe M, Sakatsume Y, Ito K, Ishi J 1994 Disturbed lipid metabolism in patients with subclinical hypothyroidism: Effect of L-thyroxine therapy. Intern Med 33:413–417.
4. Rieu M, Richard A, Rosilio M, Laplanche S, Ropion V, Fombeur JP, Berrod JL 1994 Effects of thyroid status on thyroid autoimmunity expression in euthyroid and hypothyroid patients with Hashimoto's thyroiditis. Clin Endocrinol 40:529–535.
5. Jansson R, Karlsson A, Dahlberg A 1985 Thyroxine, methimazole and thyroid microsomal autoantibody titres in hypothyroid Hashimoto's thyroiditis. Br Med J 290:11–12.
6. Romaldini JH, Werner MC, Rodrigues HF, Teixeira VL, Werner RS, Farah CS, Bromberg N 1986 Graves' disease and Hashimoto's thyroiditis drugs on thyroid autoantibodies levels. J Endocrinol Invest 9:233–238.
7. Chiovato L, Marcocci C, Mariotti S, Mori A, Pinchera A 1986 L-thyroxine therapy induces a fall of thyroid microsomal and thyroglobulin antibodies in idiopathic myxedema and in hypothyroid, but not in euthyroid Hashimoto's thyroiditis. J Endocrinol Invest 9:299–238.
8. Mariotti S, Caturegli P, Piccolo P, Barbesino G, Pinchera A 1990 Antithyroid peroxide autoantibodies in thyroid diseases. J Clin Endocrinol Metab 71:661–669.
9. Ito S, Tamura T, Nishikawa M 1968 Effects of desiccated thyroid, prednisolone and cloroquine on goiter and antibody titer in chronic thyroiditis. Metabolism 4:317–326.
10. Hayashi Y, Tamai H, Fakata S, Hirota Y, Katayama S, Kuma K, Kumagai LF, Nagataki S 1985 A long-term clinical, immunological and histological follow-up study of patients with goitrous chronic lymphocytic thyroiditis. J Clin Endocrinol Metab 61:1172–1178.
11. Papapetrou PD, Lazarus JM, McSween RNM, Harden R 1972 Longterm treatment of Hashimoto's thyroiditis with thyroxine. Lancet 2:1045–1048.
12. Hylander B, Rosenqvist U 1982 Time course effect of thyroxine on serum lipoprotein concentrations in hypothyroid subjects. Acta Med Scand 211:287–291.
13. Scarabottolo L, Trezzi L, Roma P, Catapano AL 1986 Experimental hypothyroidism modulates the expression of the low density lipoprotein receptor by the liver. Atherosclerosis 59:329–333.
14. Parle JV, Franklyn JA, Cross KW, Jones SR, Sheppard MC 1992 Circulating lipids and minor abnormalities of thyroid function. Clin Endocrinol 37:411–414.
15. Franklyn JA, Daykin J, Betteridge J, Hughes EA, Holder R, Jones SR, Sheppard MC 1993 Thyroxine replacement therapy and circulating lipid concentrations. Clin Endocrinol 38:453–459.
16. Arem R, Patsch W 1990 Lipoprotein and apolipoprotein levels in subclinical hypothyroidism: Effect of levothyroxine therapy. Arch Intern Med 150:2097–2100.
17. Cooper DS, Halpern R, Wood LC, Levin AA, Ridgway C 1984 L-thyroxine therapy in subclinical hypothyroidism. A double-blind, placebo-controlled trial. Ann Intern Med 101:18–24.
18. Cron P, Calazel C, Parra HJ, Hoff M, Louvet JP 1990 Decreased HDL cholesterol in subclinical hypothyroidism: The effect of L-thyroxine therapy. Clin Endocrinol 33:519–523.
19. Engler H, Riesen WF 1993 Effect of thyroid function on concentrations of lipoprotein (a). Clin Chem 39:2466–2469.
20. Werner RS, Romaldini JH, Farah CS, Werner MC, Bromberg N 1991 Serum thyroid-stimulating antibody, thyroglobulin levels and thyroid suppressibility measurement as predictors of the outcome of combined methimazole and triiodothyronine therapy in Graves' disease. Thyroid 1:293–299.
21. Ruf J, Czarnocka B, Ferrand M, Doullais F, Carayon P 1988 Novel routine assay of thyroperoxidase autoantibodies. Clin Chem 34:2231–2234.
22. Warmick GR 1986 Enzymatic methods for quantification of lipoprotein lipids. Methods Enzymol 129:101–123.
23. Mariotti S, Barbesino G, Caturegli P, Atzeni F, Manetti L, Marinò M, Grasso L, Velluzzi F, Loviselli A, Pinchera A, Martino E 1994 False negative results observed in anti-thy-

roid peroxidase autoantibody determination by competitive radioimmunoassays using monoclonal antibodies. Eur J Endocrinol 130:552–558.
24. Knobel M, Barca MF, Pedrinola F, Medeiros-Neto G 1994 Prevalence of anti-thyroid peroxidase antibodies in autoimmune and nonautoimmune thyroid disorders in a relatively low-iodine environment. J Endocrinol Invest 17:837–842.
25. Mariotti S, Caturegli P, Piccolo P, Barbesino G, Pinchera A 1990 Antithyroid peroxidase autoantibodies in thyroid diseases. J Clin Endocrinol Metab 71:661–669.
26. Volpé R 1994 Evidence that the immunosuppressive effects of antithyroid drugs are mediated through actions on thyroid cell, modulating thyrocyte-immunocyte signaling: A review. Thyroid 2:217–223.
27. Hashizume K, Ichikawa K, Sakurai A, Suzuki S, Takeda T, Kobayashi M, Miyamoto T, Arai M, Nagasawa T 1991 Administration of thyroxine in treated Graves' disease. Effects on the level of antibodies to thyroid-stimulating hormone receptors and on the risk of recurrence of hyperthyroidism. N Engl J Med 324:947–953.
28. Harbour DV 1991 The hormones of the hypothalamic-pituitary-thyroid axis and their receptors in the immune system. Adv Neuroimmunol 1:204–213.
29. Kruger TE, Smith LR, Harbour DV, Blalock JE 1989 Thyrotropin and endogenous regulator of the in vitro immune response. J Immunol 142:744–747.
30. Chiovato L, Vitti P, Lombardi A, Kohn LD, Pinchera A 1985 Expression of the microsomal antigen on the surface of continuously cultured rat thyroid cells is modulated by thyrotropin. J Clin Endocrinol Metab 61:12–16.
31. Althaus BU, Staub HB, Ryff AS, Oberhansli A, Stahelin HB 1988 LDL/HDL changes in subclinical hypothyroidism: Possible risk factors for coronary heart disease. Clin Endocrinol 28:157–163.
32. Lithell H, Boberg J, Hellsing K 1981 Serum lipoprotein and apolipoprotein concentrations and tissue lipoprotein lipase activity in overt and subclinical hypothyroidism: The effect of substitution therapy. Eur J Clin Invest 11:3–10.
33. Lam KSL, Chan MK, Yeung RTT 1986 High-density lipoprotein cholesterol, hepatic lipase and lipoprotein lipase activities in thyroid disfunction-effects of treatment Q J Med 59:513–520.
34. Drexhage HA, Bottazzo GF, Doniach D, Bitensky L, Chayen J 1980 Evidence for thyroid growth-stimulating immunoglobulin in some goitrous thyroid diseases. Lancet 2:287–292.
35. Vitti P, Chiovato L, Tonacchera M, Bendinelli G, Mammoli C, Capacciolo A, Fiore E, Pretell E, Pinchera A 1994 Failure to detected thyroid growth-promoting activity in immunoglobulin G of patients with endemic goiter. J Clin Endocrinol Metab 78:1020–1025.
36. Staub JJ, Althaus BU, Engler H, Ryff AS, Trabucco P, Marquard K, Burghardt D, Girard J, Weintraub BD 1992 Spectrum of subclinical and overt hypothyroidism: Effect on thyrotropin, prolactin, and thyroid reserve, and metabolic impact on peripheral target tissues. Am J Med 92:631–642.

Address reprint requests to:
Dr. João H. Romaldini
Department of Endocrinology
Hospital do Servidor Publico Estadual-IAMSPE
C.P. 8570-01000 São Paulo, SP Brazil