ORIGINAL ARTICLE

MANAGEMENT OF OVERT AND SUBCLINICAL HYPOTHYROIDISM

FACTORS INFLUENCING L-THYROXINE DOSAGE

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Abstract With the aim of establishing optimal dosage schedules, 171 women with either overt (OH, n = 80) or subclinical (SCH, n = 91) hypothyroidism were assessed before and 6 months after starting L-thyroxine (LT4) replacement therapy. Each group was further classified into four subgroups according to post-therapy serum TSH level, as follows: A) complete suppression; B) partial suppression; C) normal range and D) above normal range (insufficient response). In all subgroups, LT4 doses were higher for OH than for SCH, whether expressed as total daily dose (µg) or as a function of either actual or ideal body weight (µg/kg BW). In OH, LT4 dose was higher for subgroups A or B as compared with either C or D. In SCH, subgroup A received a larger dose than the other subgroups. Post-treatment serum thyroxine levels showed the same pattern for both OH and SCH. Mean LT4 dose was similar in patients with high and normal antithyroid antibodies and in patients with goiter and in those without it. In goitrous patients thyroid volume decreased in subgroup B, particularly in those patients that had elevated antithyroid antibodies, but not in subgroup C. In OH patients a significant negative correlation was found between daily LT4 dose per kg actual BW and actual BW, especially in subgroup C for patients with a body mass index > 27 kg/cm^2 (r = - 0.90, p < 0.001). In subgroup C of the SCH group, a negative correlation between LT4 dose and age was noticed. Both in OH and in SCH, LT4 dose per kg actual BW required to obtain a serum TSH within the normal range was lower in women with a body mass index (BMI) > 27 kg/m^2 than in those with a BMI ≤ 27 kg/m^2. LT4 doses for subgroup C did not differ from those needed in hypothyroid patients with previous Graves' disease, in either OH or SCH patients.

Resumen ***Tratamiento del hipotiroidismo clinico y subclínico. Factores que influencian la dosificación de levotiroxina.*** Con el objeto de establecer regímenes óptimos de dosificación, se evaluaron mujeres con hipotiroidismo clínico (OH, n = 80) o subclínico (SCH, n = 91), antes y 6 meses después de comenzar terapia de reemplazo con levotiroxina (LT4). Cada grupo fue clasificado en 4 subgrupos según la TSH sérica post-tratamiento, como sigue: A) supresión completa; B) supresión parcial; C) normalización; D) supranormal (respuesta insuficiente). Para los 4 subgrupos las dosis de LT4 fueron superiores en OH que en SCH tanto en valores de dosis diaria total (µg) como en dosis por unidad de peso real o ideal (µg/kg). En OH la dosis fue superior para los grupos A y B que para los grupos C y D. En SCH en el subgrupo A la dosis fue superior a la de los otros subgrupos. Los niveles de tiroxina sérica post-tratamiento fueron semejantes en OH y SCH. La dosis media de LT4 fue similar en pacientes con o sin anticuerpos antitiroideos elevados y en pacientes bociosas y no bociosas. Se observó una disminución del volumen tiroideo en pacientes bociosas con supresión parcial, mayor en aquellas con anticuerpos antitiroideos elevados, que no se observó en el subgrupo C. Se encontró una significativa correlación negativa entre peso corporal real y dosis diaria de LT4 por kg de peso real en OH, especialmente en el subgrupo C con BMI > 27, (r = - 0.90; p < 0.001), y una significativa correlación negativa entre dosis de LT4 y edad en SCH en el subgrupo C. Tanto en OH como en SCH la dosis por kg de peso real requerida para mantener la TSH dentro del rango normal fue menor en mujeres con BMI > 27 kg/m^2. Tanto en OH como en SCH, las dosis de LT4 del subgrupo C no difirieron de las requeridas por pacientes hipotiroideas con antecedentes de enfermedad de Graves.

Key words: hypothyroidism, L-thyroxine

It is currently accepted that thyroxine (LT4) is the agent of choice for hormonal replacement therapy in hypothyroidism[1-3]. In contrast with triiodothyronine administration,

that may lead to unappropiately high serum levels in the postabsorptive period, LT4 admi-nistration allows an adequate supply of triiodothyronine with nearly constant serum levels through peripheral deiodination[1, 2, 4].

Several factors have been proposed as important to determine optimum LT4 dosage, among them actual body weight[1, 5, 6], ideal body weight[2], pretreatment serum TSH levels[7], previous Graves' disease[2, 8, 9], age[10, 12], concurrent

conditions[6], duration of thyroid disease[6] and thyroxin bioavailability[5]. However, no consensus has still been reached about the relative importance of these factors.

When LT4 is prescribed according to BW, the use of actual BW[1, 6] has been proposed, although ideal BW may be better for obese patients[2]. On the other hand, some specialists prescribe LT4 in doses unrelated to BW[13, 14].

Dosage can also vary according to the treatment goal concerning serum TSH level, either to keep it within the normal range or partially suppressed, the latter being suggested when goiter is present[15, 16]. In goitrous patients, conflicting results have been reported[1]. The role of TSH in goiter development in autoimmune thyroiditis is also unsettled[17].

The main goals of the present study were: I. To assess the value of pretreatment TSH level, in particular as related to LT4 dosing differences between OH and SCH. II. To evaluate the relationship between LT4 dose and both actual and ideal BW. III. To compare LT4 doses administered to goitrous and non-goitrous hypothyroid patients, assessing whether therapy should aim at partial TSH suppression, as indicated by reduction in thyroid volume.

Furthermore, other factors potentially affecting LT4 dose, like age and presence of autoimmune thyroiditis were assessed and a comparison between the studied group and a group with previous Graves' disease was performed.

Materials and Methods

To avoid possible sex-linked variability, only women who had overt or subclinical hypothyroidism were included. Criteria for classification of patients were as follows: for OH, pre-treatment TSH > 20.0 µUI/ml and total serum thyroxine below normal levels (< 4.5 µg/dl) and for SCH, pretreatment TSH > 6.0 < 20.0 µUI/ml and total serum thyroxine within the normal range. On admission to the study, patient's history was taken, a physical examination was performed and each patient answered a questionnaire about hypothyroid symptoms (see below), medications and lifestyle. None of the patients was pregnant at admission to the study. Five patients who became pregnant during the study were excluded from it. Women included in the study were either non-smokers or smokers of less than 20 cigarettes per day. Patients included in the study had not received thyroid hormones, amiodarone or other iodinated compounds during at least 6 months before the study period. None of the patients had a history of severe cardiac, hepatic, renal or respirtory diseases. No patient suffered from insulin-dependent diabetes mellitus. During the study patients did not receive corticosteroids, estrogens or amiodarone. Compliance with treatment was adequate in all patients. Patients with known previous hyperthyroidism, patients with mild subclinical hypothyroidism (TSH > 4.5 ≤ 6.0 µUI/ml), patients with mild overt hypothyroidism (TSH ≥ 20.0 µUI/ml with normal thyroxine serum levels), patients with subacute thyroiditis, and patients with secondary hpothyroidism were excluded. Similarly, data from ten women that did not complete the study for private reasons are not included.

Finally, the group under study included 171 women with an age range of 18 to 72 years old, all of them in good general health. Eighty women (aged 47.1 ± 11.9 years) had OH caused by Hashimoto's thyroiditis (n = 31, 23 of them goitrous), non-goitrous hypothyroidism (n = 29) and surgery of diffuse or nodular goiter (n = 20; 10 with recurrent goiter). Ninety-one women (aged 39.8 ± 12.2 years old) suffered from SCH caused by Hashimoto's thyroiditis (n = 48, 26 of them goitrous), non-goitrous hypothyroidism (n = 17), surgery for diffuse or nodular goiter (n = 10; 5 with recurrent goiter) and simple goiter with normal antimicrosomal fraction antibodies (TMAb; n = 16).

For dose comparisons with hypothyroidism following Graves' disese, a control group was available. This group was made up of 39 women with diagnosed Graves' disease treated at least 18 months before with either surgery or radioactive iodine, who had SCH or OH as defined above and managed with a constant LT4 dose by at least 6 months and current normal serum TSH.

Blood tests, thyroid volume and ideal BW calculation

Blood samples for laboratory tests were obtained after an overnight fast and before ingestion of the daily LT4 dose. The following determinations were performed: 1) Total serum thyroxine by RIA (reference values 4.5 to 12.5 µg/dl); 2) serum TSH by chemoluminiscence (reference values 0.3 to 4.5 µUI/ml); 3) TMAb by agglutination (normal value: antibody titers below 1/100).

Thyroid volume was calculated according to Yokoi's method. The volume of each thyroid lobe and the ithsmus was measured by Ueda's technique[18] as previously reported[19, 20].

Calculation of ideal BW was performed with Hamwi's equation[21].

LT4 administration and follow up

Patients were instructed to take LT4 in the fasting state, since absorption is greater in this condition[1, 5].

The initial LT4 daily dose for SCH was 50 to 100 µg. Patients were followed up on a monthly basis, and adverse effects were looked for, namely cephalea, insomnia, nervousness, tachycardia and nocturnal extrasystolia. If three or more of these symptoms were present, the daily dose was lowered by 25 µg and remained at the new level until six months of treatment elapsed. If, despite dose reduction, intolerance persisted, a cardiac examination was requested to identify possible heart disorders. In this group, no cardiac disease was detected; therefore, patients were kept on the lower dose regime. All dose modifications were carried out at least 3 months before the final evaluation at the end of the 6 months period. At this time, treatment was assessed through serum thyroxine and TSH determinations.

Taking into account the reduced thyroxine metabolism reported in OH[22], patients belonging to this group at first received LT4 doses of 50 µg daily, increased by 25 to 50 µg every 4 to 8 weeks as indicated by clnical response. OH was assessed as recommended by Cooper[13], according to a score based on a previously reported statistical method[23]. Patients were asked about six symptoms, namely dry skin, constipation, poor energy, easy fatigability, cold intolerance and muscle cramps. During follow up, the subject's answers to questions about the above mentioned symptoms were rated as follows: no change, 0; improvement of a symptom, +1; disappearance, +2; worsening, -2; and appearance of a new symptom, -1. Possible overdosing was monitored as explained in SCH. If necessary, dose was lowered by 25 µg/day and kept on that level until the end of the 6-months treatment period. If symptoms persisted despite dose reduction, a cardiological examination

was requested. In this group 3 patients needed further dose reduction for the remaining period by an additional 25 to 50 µg/day because of cardiac disease. All dosage adjustements were performed at least 3 months before the last evaluation.

Assessment of the response to treatment

The study was conducted for six months. After the treatment period was completed, both OH and SCH patients were divided into four subgroups each, according to serum TSH level at that time, as follows:

A) Total suppression   (TSH < 0.10 µUI/ml)
B) Partial suppression   (TSH 0.10 to 0.30 µUI/ml)
C) TSH within the normal range (TSH 0.31 to 4.50 µUI/ml)
D) Insufficient response   (TSH > 4.50 µUI/ml)

For both groups the responses of overweight patients (BMI > 27 kg/m^2) and normal weight patients (BMI ≤ 27 kg/m^2) were compared.

Patients were classified as either non-goitrous (n = 91; 47 OH and 44 SCH) or goitrous (n = 80; 33 OH and 47 SCH) if thyroid volume was above 18.0 ml[10] or thyroid nodules were present.

For assessing the influence of high TMAb, a total of 164 patients with OH and SCH were included. At the beginning of the study, 79 patients had TMAb titers ≥ 1/100 and 92 TMAb titers within the normal range. Seven patients whose TMAb were initially within the normal range and increased above it during the study were not included in the comparison.

Statistical analysis

Statistical analysis was performed with a standard software (GraphPad Prism 2.0). For comparisons of three or more groups, an one way analysis of variance, followed by a Tukey's test when indicated, was used. For comparisons between two groups, an unpaired, two tailed Student's *t* test was applied. Linear regression was employed to assess the correlation between age and LT4 dose, and between either actual or ideal body weight and LT4 dose. Results are expressed as means ± SD. A p value < 0.05 was considered significant.

Results

Serum TSH and T4 concentrations

Pretreatment TSH levels did not differ among subgroups in either OH or SCH (in µUI/ml, for OH, A = 57.3 ± 22.7; B = 62.00 ± 32.6; C = 54.00 ± 28.8; D = 64.8 ± 32,1; p > 0.05; for SCH, A = 8.98 ± 4.11; B = 8.85 ± 5.97; C = 10.26 ± 4.45; D = 11.21 ± 5.20; p > 0.05).

Similarly, pre-treatment serum thyroxine levels was similar for the subgroups of both OH and SCH (in µg/dl, OH: A = 3.24 ± 2.22; B = 2.81 ± 1.10; C = 3.21 ± 1.70; D = 2.92 ± 1.10; p > 0.05. SCH: A = 5.52 ± 1.44; B = 6.07 ± 1.44; C = 5.74 ± 1.21; D = 5.51 ± 0.94; p > 0.05).

For both OH and SCH patients, post-treatment serum thyroxine concentrations were higher in those with complete and partial TSH suppression (subgroups A and B) than in those with normal or above normal TSH (groups C and D); p < 0.01 (Table 1). There were no significant differences in post-treatment serum thyroxine between OH and SCH for any given subgroup (p > 0.05).

Total LT4 daily dose

For all four subgroups, the mean LT4 daily dose was higher in OH than in SCH patients (p > 0.001; Table 2). In OH patients, LT4 did not differ between subgroups A or B, nor between subgroups C and D (p > 0.05). However, LT4 dose was higher for both subgroups A and B than for subgroups C and D (p < 0.01). In SCH patients, the LT4 dose that caused complete suppression was higher than those of subgroups C and D (p < 0.02).

In OH, a significant positive correlation was found between LT4 total daily dose and actual BW (r = 0.44; p < 0.05). This correlation was not significant in SCH patients. Neither OH nor SCH showed a significant correlation between LT4 total daily dose and ideal BW.

Daily LT4 dose per kg actual and ideal body weight

As shown in Table 3, LT4 dose per kg actual BW was consistently higher in all OH subgroups than in the respective SCH subgroups. Within the OH group the

TABLE 1.– Post-treatment serum thyroxine in patients with overt (OH) and subclinical hypothyroidism (SCH) classified according to post-treatment serum TSH concentration

	n	OH* Serum thyroxine (µg/dl)	n	SCH** Serum thyroxine (µg/dl)	p
A	12	11.11 ± 2.50	16	10.38 ± 1.50	NS
B	17	10.30 ± 1.60	22	10.00 ± 2.01	NS
C	33	7.96 ± 0.88	43	8.51 ± 1.38	NS
D	18	8.07 ± 1.23	10	7.77 ± 1.24	NS

* A vs B, NS; A vs C, p < 0.01; A vs D, p < 0.01; B vs C, p < 0.01; B vs D, p < 0.01; C vs D, NS
** A vs B, NS; A vs C, p < 0.01; A vs D, p < 0.01; B vs C, p < 0.01; B vs D, p < 0.01; C vs D, NS

TABLE 2.– *Total daily dose in patients with overt (OH) and subclinical hypothyroidism (SCH) classified according to post-treatment serum TSH concentration*

	n	OH* LT4 dose µg	n	SCH** LT4 dose µg	p
A	12	158. 7 ± 29.6	16	109.7 ± 32.4	< 0.001
B	17	144.4 ± 27.9	22	85.5 ± 27.3	< 0.001
C	33	125.1 ± 17.7	43	80.5 ± 27.1	< 0.001
D	18	122.5 ± 20.8	10	80.0 ± 20.5	< 0.001

* A vs B, NS; A vs C, p < 0.001; A vs D, p < 0.01; B vs C, p < 0.01; B vs D, p < 0.01; C vs D, NS
** A vs B, p < 0.02; A vs C, p < 0.02; A vs D, p < 0.02; B vs C, NS; B vs D, NS; C vs D, NS

TABLE 3.– *Daily dose per kg actual BW in patients with overt (OH) and subclinical (SCH) hypothyroidism classified according to post-treatment serum TSH concentration*

	n	OH* LT4 dose µgd	n	SCH** LT4 dose µgd	p
A	12	2.40 ± 0.54	16	1.64 ± 0.49	< 0.001
B	17	2.26 ± 0.48	22	1.31 ± 0.40	< 0.001
C	33	1.88 ± 0.39	43	1.23 ± 0.39	< 0.001
D	18	1.82 ± 0.52	10	1.16 ± 0.43	< 0.001

* A vs B, NS; A vs C, p < 0.01; A vs D, p < 0.05; B vs C, p < 0.01; B vs D, p < 0.01; C vs D, NS
** A vs B, NS; A vs C, p < 0.01; A vs D, p < 0.05; B vs C, NS; B vs D, NS; C vs D, NS

TABLE 4.– *Daily LT4 dose per kg of actual and ideal BW of OH and SCH patients according to serum TSH response and BMI. The upper of each pair is dose per kg actual BW and the lower dose per kg ideal BW*

		n	LT4 µg/kg BMI > 27	n	LT4 µg/kg BMI ≤ 26	p
OH						
A	Actual BW	4	2.14 ± 0.63	8	2.50 ± 0.51	NS
	Ideal BW		2.85 ± 0.48		2.58 ± 0.57	NS
B	Actual BW	5	2.01 ± 0.40	12	2.37 ± 0.47	NS
	Ideal BW		2.56 ± 0.34		2.39 ± 0.41	NS
C	Actual BW	13	1.60 ± 0.27	20	2.06 ± 0.41	p < 0.05
	Ideal BW		2.29 ± 0.37		2.09 ± 0.49	NS
D	Actual BW	7	1.50 ± 0.40	11	2.02 ± 0.41	p < 0.05
	Ideal BW		2.16 ± 0.39		1.97 ± 0.41	NS
SCH						
A	Actual BW	5	1.42 ± 0.51	11	1.74 ± 0.47	NS
	Ideal BW		1.85 ± 0.71		1.76 ± 0.48	NS
B	Actual BW	8	1.18 ± 0.25	14	1.37 ± 0.45	NS
	Ideal BW		1.61 ± 0.40		1.47 ± 0.39	NS
C	Actual BW	18	1.08 ± 0.33	25	1.34 ± 0.33	p < 0.05
	Ideal BW		1.44 ± 0.39		1.27 ± 0.40	NS
D	Actual BW	5	0.96 ± 0.31	5	1.36 ± 0.48	NS
	Ideal BW		1.36 ± 0.34		1.25 ± 0.34	NS

subgroups A and B dose was significantly higher than those of subgroups C and D. In SCH patients, the dose of subgroup A was significantly higher than those of subgroups B, C and D. Other comparisons did not show differences among subgroups (Table 3).

Daily LT4 dose per kg ideal BW showed essentially the same pattern noted for daily T4 dose per kg actual BW. (OH: A: 2.67 ± 0.61; B: 2.43 ± 0.47; C: 2.21 ± 0.44; D: 2.00 ± 0.39; SCH: A: 1.79 ± 0.59; B: 1.47 ± 0.37; C: 1.34 ± 0.39; D: 1.31 ± 0.39 µg/kg). The LT4 dose insufficient for OH patients (subgroup D) was significantly higher than that of subgroup A in SCH patients (p < 0.05).

A significant correlation between daily dose per kg and actual BW was found in OH (r = -0.63; p < 0.01) but not in SCH (r = -0.27; p > 0.05).

LT4 dose and body mass index

LT4 doses accordig to high or normal BMI are shown in Table 4. For TSH normalization in women with a BMI > 27 kg/m^2, LT4 dose was significantly lower when expressed as a function of actual BW than when expressed as a function of ideal weight both for OH (1.60 ± 0.27 µg/kg vs 2.29 ± 0.37 µg/kg; p < 0.001) and for SCH patients (1.08 ± 0.33 µg/kg vs 1.44 ± 0.39 µg/kg; p < 0.001). As it could be expected, no such difference was found for women with a BMI equal to or lower than 27 kg/m^2. (OH, 2.06 ± 0.41 vs 2.09 ± 0.49 and SCH 1.34 ± 0.33 vs 1.27 ± 0.40; p > 0.05 for both).

In OH patients, a significant negative correlation was found between daily LT4 dose per kg actual BW and actual BW for subgroup C in patients with high BMI (r = - 0.90; p < 0.001). However, in subgroup C of OH patients with a BMI ≤ 27 kg/m^2 the same correlation was non significant (r = -0.27; p > 0.05). In the same subgroup, no significant correlation between daily LT4 dose per kg ideal BW and ideal BW was found (r = -0.26 for high BMI and r = -0.29 for normal BMI; p > 0.05 for both).

LT4 dose as a function of age

For subgroup C of SCH patients, a significant negative correlation was present between age and daily dose per kg of actual BW (r = - 0.54; p < 0.001). Neither in the same subgroup of OH patients (r = - 0.15; p > 0.05), nor in other subgroups was such a correlation found.

LT4 dose and goiter

For both OH and SCH, LT4 doses did not differ between goitrous (G) and non-goitrous (NG) patients, expressed as total daily dose in µg/day.

OH: A: 160.0 ± 20.2 (G) vs 154.0 ± 27.2 NG) (p > 0.05); B: 148.4 ± 25.0 (G) vs 140.2 ± 32.6 (NG) (p > 0.05); C: 125.3 ± 33.5 (G) vs 124.4 ± 17.7 (NG) (p > 0.05); D: 124.0 ± 23.5 (G) vs 120.6 ± 27.2 (NG) (p > 0.05).

SCH: A: 116.7 ± 30.2 (G) vs 105.2 ± 27.2 (NG) (p > 0.05); B: 87.1 ± 17.5 (G) vs 82.0 ± 22.1 (NG) (p > 0.05); C: 80.6 ± 30.3 (G) vs 80.0 ± 17.7 (NG) (p > 0.05); D: 84.0 ± 19.3 (G) vs 78.6 ± 18.2 (NG) (p > 0.05).

LT4 dose and antithyroid antibodies

Total daily doses were compared for each group. No difference was found in LT4 dose in either OH or SCH

TABLE 5.– *Daily LT4 dose in patients of the present series (Non-Graves disease) compared with those of patients with previous Graves' disease. Total daily doses and total daily doses per kg actual body weight are shown*

LT4 dose	n	Graves' disease	n	Non-Graves' disease	p
Overt Hypothyroidism					
(μg)	23	132.0 ± 20.0	33	125.0 ± 17.0	> 0.05
(μg/kg)		1.88 ± 0.31		1.83 ± 0.39	> 0.05
Subclinical Hypothyroidism					
(μg)	16	76.7 ± 10.2	43	80.5 ± 27.1	> 0.05
(μg/kg)		1.24 ± 0.31		1.23 ± 0.39	> 0.05

patients segregated according to high (H) or normal (N) TMAb titers. The dose was expressed in μg/day.

OH: A 155.2 ± 31.2 (H) vs 161.8 ± 30.3 (N) (p > 0.05); B: 150.0 ± 15.2 (H) vs 142.0 ± 25.0 (N) (p > 0.05); C: 123.8 ± 16.8 (H) vs 125.9 ± 22.3 (N) (p > 0.05); D: 123.6 ± 19.2. (H) vs 121.8 ± 23.0 (N) (p > 0.05).

SCH: A: 112.8 ± 25.0 (H) vs 107.4 ± 23.2 (N) (p > 0.05); B: 90.6 ± 22.6 (H) vs 84.3 ± 21.4 (N) (p > 0.05); C: 80.0 ± 21.9 (H) vs 81.2 ± 20.9 (N) (p > 0.05); D: 80.8 ± 17.5 (H) vs 79.4 ± 18.2 (N) (p > 0.05).

LT4 dose and thyroid volume

Goitrous patients belonging to subgroup C showed no change in thyroid volume (Δ volume = - 1.21 ± 10.8 ml; p > 0.05) regardless of TMAb titers. On the other hand, subgroup B goitrous patients showed a significant reduction in thyroid volume (Δ volume = - 6.68 ± 4.08 ml; p < 0.001). In goitrous patients belonging to subgroup B, those with high TMAb had a larger volume reduction than those with a low antibody titer (Δ volume: - 7.35 ± 3.67 ml vs -3.76 ± 2.20 ml; p < 0.02).

Comparison with hypothyroid patients with previous Graves' disease

LT4 doses required for attaining normal TSH concentrations in the present study cohort (subgroup C: OH, n = 33, SCH n = 43) were compared with those required in patients with previous Graves' disease and either OH (n = 23) and SCH (n = 16). As shown in Table 5, no diffrence was found for either group.

Discussion

It has recently been recommended that TSH should be lowered to values within the range 0.5 to 3.0 μUl/ml in non-goitrous hypothyroid patients, and to suppressed levels in goitrous hypothyroid patients[2, 3]. It is generally accepted that is not necessary to lower TSH below 0.1 μUl/ml[15, 16]. We submit that LT4 doses that lower TSH below 0.1 μUl/ml are too high, since they can cause undesirable side effects in long-term therapy, like increased left ventricular mass index, higher prevalence of atrial premature beats and enhanced left ventricular systolic function[26, 27] and probably osteopenia[28].

In agreement with authors pointing out that thyroxine[22] and TSH[6] determinations after 6 months of treatment are adequate for dose assessment, we chose this period for the present study.

With the standard dose of 100 μg/day the serum response was not the same for OH and SCH patients. The percentage of patients achieving TSH values within the normal range was similar for both groups (46% for SCH and 45% for OH). However, in the OH group no patient had her serum completely suppressed with this dose; only 5% of patients attained partial supression, and the dose was insufficient for 50% of them. On the other hand, the same LT4 dose caused total suppression in 19% and partial suppression in 26% of SCH patients, while it was insufficient in only 9% of cases.

Our results show that the mean LT4 dose required to normalize or suppress serum TSH is higher for OH than for SCH patients. When expressed as a function of ideal weight, the LT4 dose that proved insufficient for OH patients was higher than the dose causing total suppression in SCH patients.

Daily thyroxine secretion is related to BW[3]. It has been reported that the daily LT4 dose required to lower serum TSH to normal or subnormal levels in hypothyroid patients is also related to BW[2, 29]. We found a highly significant negative correlation between daily LT4 dose per kg actual BW and actual BW in OH patients, particularly in patients with BMI > 27 kg/m^{2}. On the other hand, we observed a less significant positive correlation between total daily LT4 dose and actual BW. It may be submitted than an influence of fat body mass is noticeable but smaller and less variable than that of lean body mass.

Furthermore, we did not find a significant correlation between LT4 dose and ideal BW for either normal or obese patients. Therefore, we disagree with authors who propose dosing according to ideal BW in obese patients[2] as well as with those who relate LT4 dose only to lean body mass and age[30].

The SCH subgroup that reached normal TSH values at the end of the study showed a significative correlation between LT4 dose and age (r = -0.54). This may be due to both a reduction in peripheral thyroxine degradation and to an increased adenohypophyseal sensitivity to LT4 associated with aging[31]. Seemingly, these age-dependent changes might be more apparent in SCH than in OH patients.

In OH patients the LT4 dose required to partially suppress TSH was higher than the dose needed for reaching TSH values within the normal range. Therefore, when aiming at partial TSH suppression –desirable according to present data– goitrous OH patients should receive a higher dose than non-goitrous OH patients.

It has been reported that the LT4 dose will be lower for hypothyroid patients with previously diagnosed Graves' disease than for those not diagnosed with this disease[8, 9]. Our results show no such difference in the required LT4 dose for either OH and SCH patients. The reported frequency of early reversible hypotyroidism[32] should be taken into account.

While it has been pointed out that thyroid volume is not TSH-dependent in autoimmune thyroiditis[17], present data show that patients undergoing the largest thyroid volume decreases were those with high circulating TMAb titers that had their TSH suppressed by LT4 therapy.

Kabadi's study is often quoted in support of the notion that OH therapy demands higher LT4 doses than SCH therapy[1, 2, 6]. On the other hand, in a 1995 study by Müller et al.[14], neither a correlation between the severity of hypothyroidism and the LT4 daily dose required to obtain normal TSH values, nor a different daily LT4 dose for OH and SCH were found in female patients. Our data clearly support that SCH patients should be usually managed with lower LT4 doses than OH patients.

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