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Research paper

The serum triiodothyronine to thyroxine (T3/T4) ratio in various thyroid disorders and after Levothyroxine replacement therapy

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ABSTRACT

In order to examine the significance of differences in the triiodothyronine/thyroxine (T3/T4) ratio in the achievement of euthyroidism and in different thyroidal diseases, we studied 1050 subjects: 233 were euthyroid (Eu), 239 hypothyroid (Hypo) with initial TSH levels >15 mU/L, 273 hypothyroid on substitution therapy with L-thyroxine alone and TSH values of 0.35-3.5 mU/L, (hypoRx), 236 hyperthyroid (hyper) and 69 in the acute phase of subacute thyroiditis De Quervain's (DQ). The ratio of T3/T4 was calculated using the conventional values. Results: The values of T3/T4 ratio in the various categories were: Eu= 15.89, Hypo= 24.12, hyper= 19.57, hypoRx= 13.42, DQ= 15.16. The T3/T4 ratio was lower in the hypoRx group than in the EU group (P <0.001), although neither TSH values nor T3 values showed any differences between these two groups, whereas T4 levels were significantly higher in the hypoRx group (Eu= 7.99±1.46, hypoRx = 9.11±1.58, P< 0.001). The T3/T4 ratio in the DQ group was comparable to that of the Eu group, but significantly lower than the hyper group (P=0.95 between Eu and DQ, P<0.001 between DQ and hyper). Conclusions: These findings indicate that in hypothyroid patients, L-T4-replacement that is sufficient to maintain a normal serum TSH is accompanied by a serum T4 that is higher than in normal individuals and may not result in an appropriately normal serum T3 concentration. In Thyrotoxicosis, a ratio of total T3/T4 >18.9 suggests Graves' disease or toxic multinodular goiter whereas T3/T4 <16 suggests thyroiditis (subacute or silent).

Key words: T3/T4 ratio, Hypothyroidism, Destructive thyroiditis, Replacement therapy

INTRODUCTION

In the euthyroid state, the thyroid gland produces the entirety of the body's thyroxine (T4) (about 80-90 μg/d), but only 20% of the body's triiodothyronine (T3) In fact, the total integrated daily production of T3 in the body is ≃32 mcg: 8 mcg secreted directly from the thyroid gland and the rest (≃ 24 mcg) originating from peripheral deiodination of the outer ring of T4 by type I 5'-deiodinase, mainly in the liver and the kidney[1]. However, in hyper- and hypo-thyroid states, a higher fraction of total plasma T3 is produced by the thyroid gland[2].

T3 represents the active form of thyroid hormones.

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It increases cardiac output, cardiac contractility and heart rate and decreases systemic vascular resistance[3].

In healthy individuals the relationship between T3 and T4 is finely controlled in such a way that differences in hormone activity due to the wide range of serum T4 among normals may be buffered by systematic adjustment of the T3/T4 ratio. Those with the highest T4 appear to maintain euthyroidism with a minimal T3/T4 ratio. The remainder, with T4 levels towards the lower limit of normal, are subject to a progressive increase in the T3 fraction and may depend on it to remain euthyroid.

Thyroxine, in the form of Levothyroxine sodium, is the most widely prescribed treatment for hypothyroidism. Combinations of thyroxine and triiodothyronine are available as synthetic preparations, but are not usually recommended. The main advantage of treatment with thyroxine is that the serum concentration of triiodothyronine, formed in extrathyroidal tissues from the ingested thyroxine, is controlled physiologically, which may be of benefit during illness or fasting when extrathyroidal production of triiodothyronine is usually decreased[4].

Recent reports in hypothyroid patients receiving T4 replacement therapy have demonstrated T3 levels lower than those of euthyroid subjects, even when the T4 levels are in the high-normal range and TSH is suppressed[5].

The aim of this study was to evaluate the T3/T4 ratio in normal subjects and compare them with those in the active phase of hyper- and hypothyroidism, in the active phase of destruction-induced thyrotoxicosis and during thyroxine replacement for primary hypothyroidism.

SUBJECTS AND METHODS

We analysed retrospectively the data of patients of the outpatient endocrine clinic of Athens Medical Centre Hospital.

We excluded patients with chronic or acute diseases, patients with iodopenic or nodular goiter, those on a weight-reducing diet, pregnant women, and patients taking drugs influencing thyroid function or serum hormone levels. 1050 subjects fulfilling these criteria were included:

233 were euthyroid (Eu), without goiter or thyroidal autoantibodies, (anti-TG and anti-TPO <2 U/L)- 171 females/ 62 males;

239 were hypothyroid (hypo, TSH >15 mU/L) - 201 females/ 38 males;

236 were hyperthyroid (hyper) - 172 females/64 males; these all had Grave's disease or toxic multinodular goiter;

273 were on L thyroxine replacement therapy hypoRx for hypothyroidism and their TSH levels were 0.35-3.5 mU/L - 256 females/17 males;

69 were in the acute phase of subacute thyroiditis De Quervains (DQ)- 56 females/ 13 males.

Another group of 251 subjects post thyroidectomy for carcinoma, under thyroxine therapy and with suppressed TSH levels (< 0.2 mU/L), but normal T3 and T4 levels, was used to determine whether serum TSH has any effect on peripheral deiodination of T4.

The age and the body mass index (BMI) of included patients, according to gender and thyroid status, are depicted in Table 1. As shown in this table, subjects from a wide range of age and body weight groups were used.

Serum levels of T4/T3 were determined with one-site chemiluminescent immunoassay and TSH with two-site chemiluminescence (Nichols Institute Diagnostics, Ca, USA) and the T3/T4 ratio was calculated. The normal ranges for our laboratory are: For T4: 5.2-12.5 μg/dl, for T3: 70-190 ng/dl, for TSH: 0.3-4.5 mU/L. Antithyroid antibodies were determined by two-site chemiluminescent immunoassay. For anti-TG and for anti-TPO our normal values were <2 U/L. Statistical analysis was performed with the statistical program SPSS v 8.0. The statistical methods used were one way ANOVA, paired Student's t-test. A two-tailed $P < 0.05$ value was utilised throughout as a criterion for any result that was statistically significant.

RESULTS

T-test in all the studied groups between males and females showed no statistical difference in the values of T3, T4 and TSH (Table 2).

T4 levels ($x \pm sd$), as expected, were elevated in hyperthyroid subjects (18.64 ± 5.09), as well as in those

Table 1. BMI in Kg/m^2 and age of studied subjects according to thyroid status (Values are: mean±sd, range).

Group	Females			Males		
	n	AGE	BMI	n	AGE	BMI
1. Hyperthyroid	172	44.7±14.3 (14-75)	25.02±4.62 (17.3-42.7)	64	48.4±15.5 (18-85)	25.3±2.93 (17.2-31.4)
2. Eurthyroid	171	34.2±11.9 (11-73)	32.73±5.68 (21.1-48.6)	62	35.4±13.6 (13-68)	37.12±6.30 (25.2-65.2)
3. Hypothyroid	201	46.5±14.6 (9-84)	28.77±5.77 (16.1-51.5)	38	51.9±15.5 (21-89)	29.35±4.63 (22.1-45.8)
4. Hypothyroid on L-Thyroxine replacement therapy	256	45.9±13.3 (11-79)	33.23±7.25 (19.7-60.1)	17	47.1±13.9 (19-81)	32.92±7.03 (24.8-50.8)
5. Subacute thyroiditis	56	47.6±10.1 (28-70)	23.51±3.91 (20.2-34.1)	13	47.4±10.5 (35-74)	25.61±4.31 (19.9-33.9)

Table 2. Plasma levels of T4* in μg/dl, T3* in ng/dl and TSH in mU/L according to gender

Group	Females				Males			
	n	T4	T3	TSH	n	T4	T3	TSH
1. Hyperthyroid	172	18.5±5.2	353.1±144.3	0.05±0.04	64	19.1±4.9	395.5±154.5	0.05±0.05
2. Eurthyroid	171	8.0±1.5	123.7±24.4	1.63±0.78	62	7.9±1.5	126.5±24.5	1.62±0.74
3. Hypothyroid	201	3.6±1.6	75.1±33.4	43.7±24.4	38	3.3±1.8	70.9±25.9	46.9±29.5
4. On hypothyroid T4 replacement	256	9.1±1.6	119.6±23.5	1.54±1.13	17	8.8±1.3	124.1±26.9	1.56±1.20
5. Subacute thyroiditis	56	14.3±5.2	220.2±98.2	0.19±0.34	13	17.2±5.3	238.6±64.8	0.06±0.05

*For conversion to SI units multiply by 12.87 for T4 and 0.01536 for T3. No differences between males and females were disclosed.

with subacute thyroiditis (14.86±5.30), and decreased in hypothyroidism (3.58±1.67). T4 levels were higher in subjects on Thyroxine replacement (9.11±1.58) than in euthyroids (7.99±1.46) (mean difference 1.12 μg/dl, P< 0.001), Table 3.

T3 serum levels (Table 3) were increased in hyperthyroid subjects and in those with subacute thyroiditis and decreased in hypothyroidism. There was no difference in T3 levels between euthyroids (124.47±24.37 ng/dl) and those on Thyroxine replacement (119.85±23.68 ng/dl, P= 0.90).

TSH levels (table 3) were increased in hypothyroid subjects and suppressed in hyperthyroid and those with DQ. There was no statistically significant differ-

Table 3. Serum levels of T4 in μg/dl[1], T3 in ng/dl[1] and TSH in mU/L (both genders)

Group	n	T4 Mean ± SD	P * for T4	T3 Mean ± SD	P ** for T3	TSH Mean ± SD	P for TSH
1. Hyperthyroid	236	18.64±5.09	0.000	365.31±147.99	0.000 *	0.005±0.053	NS vs group 5
2. Eurthyroid	233	7.99±1.46	0.000	124.47±24.37	0.000 # NS §	1.63±0.77	NS vs group 4
3. Hypothyroid	239	3.58±1.67	0.000	74.46±32.32	0.000 *	44.23±25.23	0.000 vs all groups
4. On Thyroxine replacement	273	9.11±1.58	0.000	119.85±23.68	0.000 # NS •	1.54±1.13	NS vs group 2
5. Subacute thyroiditis	69	14.86±5.3	0.000	223.66±92.72	0.000 *	0.17±0.34	NS vs group 1

*: compared to all the other subgroups for T4.

**: compared to all the other groups, # compared to groups 1.3.5, § compared to group 4, • compared to group 2.

[1]For conversion to SI units multiply by 12.87 for T4 and 0.01536 for T3.

ence in TSH levels between hyper and DQ (P= 0.56), nor between euthyroids and those on Thyroxine replacement (P= 0.90).

T3/T4 ratios are depicted in Table 4 (Figure 1). There is a very clear and highly significant difference between the 5 subgroups (Table 5), except between the euthyroids and those with subacute thyroiditis (P= 0.95).

Comparison of the T3/T4 ratio between normal subjects and euthyroids under L-thyroxine replacement has a mean difference of 2.46 (P= 0.002) and a 95% confidence interval 0.68 to 4.25.

Thyroid serum hormone levels in subjects post thyroidectomy for carcinoma and with suppressed TSH were: T4= 9.9±1.5, T3= 125.4±28.1, TSH= 0.1±0.08 and the T3/T4= 12.77. This ratio was lower than the ratio T3/T4 of subjects on replacement therapy and normal TSH levels, but the difference had no statistical significance (P= 0.88).

Finally, we distributed the T3/T4 ratio and T3 levels of the normal subjects and of those on L-Thyroxine replacement therapy into 10th, 25th, 50th and 95th percentiles (Tables 6 and 7). 34 subjects (12.5% of the entire group, 32 females) on replacement therapy with L- thyroxine and normal TSH levels had both T3 and T3/T4 below the 10th percentile of euthyroid subjects. More detailed characteristics of this subgroup are depicted in Table 8.

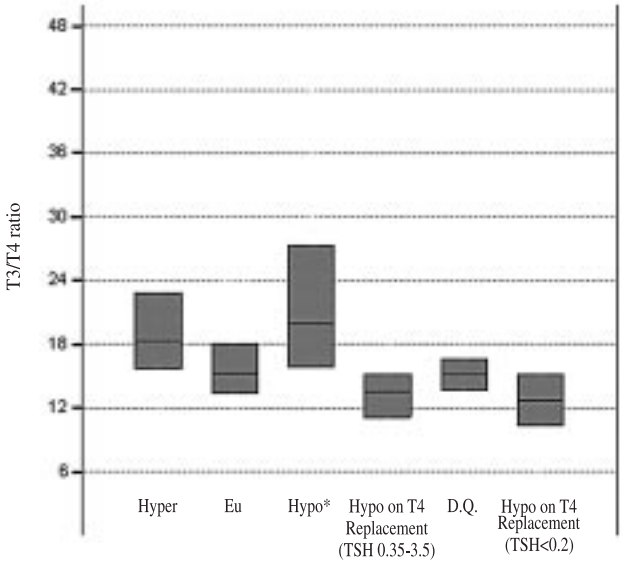

Figure 1. Box plots of T3/T4 ratio in the various thyroid disorders. Median values (horizontal lines) ±1 SD.

DQ: Subacute Thyroiditis

*: TSH values >15 mU/L

DISCUSSION

The T3/T4 ratio is a simply calculated index reflecting thyroid function and the action of hormones on the tissues. It is a very useful aid for the diagnosis of borderline thyrotoxicosis, euthyroid sick syndrome[2], adequate or not replacement therapy, the action of different drugs on thyroid function and/or hormone

Table 4. T3/T4 ratio in the various groups. T3 is expressed in ng/dl* and T4 in μg/dl*

	Mean	± SD	95% interval		Min	Max
1. Hyperthyroid	19.57	5.51	18.86	20.27	10.04	44.35
2. Euthyroid	15.89	3.56	15.43	16.35	9.13	31.15
3. Hypothyroid	24.12	13.45	22.40	25.83	9.41	100.00
4. On Thyroxine replacement	13.42	3.02	13.07	13.79	7.11	25.00
5. Subacute thyroiditis	15.16	2.95	14.45	15.87	8.32	21.57

* For conversion to SI units multiply by 12.87 for T4 and 0.01536 for T3.

Table 5. ONE WAY ANOVA for T3/T4 ratio between euthyroid subjects and the 4 other subgoups

	Mean differ.	**± SD**	**P**	**95% conf. interval**	
1. Hyperthyroid	-3.6746	.677	0.000	-5.5222	-1.8269
2. Hypothyroid	-8.2220	.675	0.000	-10.0639	-6.3801
3. On Thyroxine replacement	2.4650	.654	0.002	.6807	4.2494
4. Subacute thyroiditis	.7351	1.005	NS	-2.0069	3.4771

POSTHOC= TUKEY, BTUKEY BONFERRONI ALPHA (0.05)

Table 6. Absolute values and Percentiles of T3/T4 ratio in euthyroid subjects and hypothyroids on Thyroxine replacement and normal TSH levels

	Euthyroids	Euthyroids on L-thyroxine replacement
Mean	15.89	13.43
Median	15.37	13.57
Minimum	9.13	7.11
Maximum	31.15	25.00
Percentiles	10th 11.99	10th 9.54
	25th 13.40	25th 11.12
	50th 15.37	50th 13.57
	95th 22.19	95th 18.62

Table 7. Absolute values and Percentiles of T3 (ng/d)l in euthyroid subjects and in hypothyroid subjects on L-Thyroxine replacement and normal TSH levels

	Euthyroids	Euthyroids on L-thyroxine replacement
Mean	124.47	119.85
Median	122.00	121.00
Minimum	70.00	70.00
Maximum	190.00	186.7
Percentiles	10th 92.1	10th 90.0
	25th 108.7	25th 101.0
	50th 122.0	50th 121.0
	95th 170.0	95th 160.0

For conversion to SI units multiply by 0.01536

levels[6], iodine deficiency, thyrotoxicosis factitia and autonomous nodules of the thyroid gland. The T3/T4 ratio also has a prognostic value for the relapse of hyperthyroidism in post-treated hyperthyroid patients[7] and can distinguish a typical hyperthyroidism from destructive thyroiditis[8].

In normal subjects the T3/T4 ratio is influenced neither by the body weight nor by the physical activity level, gender, race or the blood sampling conditions. The nutritional status can influence the ratio if there is inadequate iodine intake or if the person is on a weight-reducing diet[9].

As previously mentioned, T3/T4 ratio is increased in hyperthyroidism because of the higher secretion of T3, but also in hypothyroidism because of the higher efficiency of the thyroid gland to secrete the more biologically active fraction of the hormones and the increased 5'-deiodinase tissue's activity. Additionally, in hypothyroidism T3/T4 ratio is much higher because of the pronounced decline of T4 levels.

In the acute phase of DQ, the T4 and T3 levels are usually increased and the TSH levels are suppressed, but the differences from those of hyperthyroid subjects are not clear. The T3/T4 ratio however shows a significant difference between these two groups: DQ= 15.16±2.95, 95% C.I 14.45 to 15.87 - hyper= 19.57±5.51, 95% C.I 18.86 to 20.27, P<0.001.

In this study, our effort was to establish whether or not normal TSH levels in hypothyroid patients on replacement therapy with thyroxine alone reflects euthyroidism in all cases.

There is almost universal agreement on the use of L-thyroxine alone as replacement therapy for hypothyroidism. Because of reports demonstrating that a low TSH concentration is a risk factor for the development of atrial fibrillation in the elderly[10]and a risk factor for osteoporosis and changes in the function of other target organs, such as the liver, heart and kidney[11], the American Thyroid Association was prompted to state that "the goal of therapy with L-thyroxine is to restore patients to the euthyroid state and to normalise serum thyroxine and TSH concentrations"[12], not mentioning at this time T3 levels. Although this is suitable for most patients, a small proportion of patients with hypothyroidism say that they do not feel as well as they would like while taking thyroxine in doses

Table 8. Characteristics of 34 subjects on Thyroxine replacement and normal TSH levels with T3 and T3/T4 < 10th percentile of euthyroid subjects

	Age	BMI	T4	T3	TSH	T3/T4
Mean	44.85	31.67	8.99	83.52	1.56	9.38
± SD	11.22	7.75	1.05	6.58	1.10	1.06
Min	22	20.05	7.20	70.00	0.30	7.11
Max	71	60.06	11.95	92.00	4.10	11.34

only sufficient to restore their TSH concentrations to normal and that they have a sense of well-being only if the dose of prescribed thyroxine is 25-50 μg greater than the dose needed to restore normal TSH secretion. Therefore, many physicians have been content to allow patients to have serum T4 levels at the upper normal limit or slightly higher, low serum TSH concentrations (<2 mU/L), but normal plasma T3[13].

In our study, the hypothyroid group on Thyroxine replacement had identical mean T3 concentrations with those of the euthyroid group (119.85 vs. 124.47 ng/dl), but significantly higher T4 levels (9.11 vs. 7.99 μg/dl) and a significantly lower T3/T4 ratio (13.42 vs. 15.89). This finding means that in order to achieve normal T3 levels in hypothyroid patients, we have to give higher doses of L-Thyroxine as replacement therapy.

While the debate about the correct dose of thyroxine persists, important observations have been made in rats that are possibly relevant to humans. In thyroidectomised rats, it was possible to achieve tissue euthyroidism and normal serum concentrations of T3, T4 and TSH only by administering a combination of T4 and T3. In rats given thyroxine alone, normal concentrations of triiodothyronine could not be achieved in tissues without the administration of supraphysiological doses[14].

In another study in hypothyroid humans[15], when the usual dose of L-Thyroxine was reduced by 50 μg and was replaced by 12.5 μg of triiodothyronine, significant improvement was observed in mood and neuropsychological function**.** As Silva and Larsen have shown, T4 is preferentially converted to T3 in the pituitary to a greater degree than in the other tissues, so its TSH suppressive effect is greater than its metabolic. Thus, Thyroxine replacement treatment of hypothyroid subjects aiming at a normal serum TSH value may result in undertreatment[16,17].

Following upon the previously mentioned data, the question once again arises: one hormone or two for replacement therapy?[18]

It should not be forgotten that the majority of patients taking a dose of thyroxine that satisfies the recommendations of the American Thyroid Association (normal T4 and TSH concentrations) have no complaints about their treatment. However, most international authorities suggest that we should keep TSH not just *'normal'* but *'low-normal'*, i.e. = 2.0 mU/L.

In our study, 12.5% of the hypothyroid group on thyroxine replacement therapy (the majority of them being females) and normal T4 and TSH levels, had both T3 and T3/T4 <10th percentile of euthyroid subjects. Those levels are T3 <92 ng/dl and T3/T4 <12. This finding may suggest a decreased ability of tissue T4 5'-deiodination.

In these cases, and if there are no contraindications, it is possible to replace 50 mcg of the administered thyroxine with 12.5 mcg of triiodothyronine or, as suggested by other authors, with 7.5 mcg

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