Usefulness of free thyroxine to free triiodothyronine ratio for diagnostics of various types of hyperthyroidism

Uporabnost razmerja med prostim tiroksinom in prostim trijodtironinom v diagnostiki različnih oblik hipertiroze

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Izvleček

Izhodišča: Različne oblike hipertiroze zdravimo različno. Pravilna diagnoza omogoča ustrezno zdravljenje. Klinične izkušnje kažejo, da je razmerje med prostim tiroksinom (pT_4) in prostim trijodtironinom (pT_3) pri različnih oblikah hipertiroze različno. Ker je literature na tem področju malo, smo se odločili opredeliti vlogo razmerja med pT_4 in pT_3 (pT_4/pT_3) v diagnostiki različnih oblik hipertiroze.

Metode: V retrospektivno raziskavo smo vključili 440 zaporednih bolnikov, pregledanih med februarjem in avgustom 2010, 350 žensk in 90 moških, starih med 15 in 97 let, med njimi 225 zdravih, 80 bolnikov z bazedovko (B), 48 s toksičnim adenomom (TA), 61 s hipertirotičnim Hashimotovim tiroiditisom (HHT), 17 s subakutnim tiroiditisom (ST) in 9 s hipertirozo zaradi čezmernega vnosa joda (HČVJ). Izmerili smo tirotropin (TSH), pT_4, pT_3 in ščitnična protitelesa. Izračunali smo razmerje pT_4/pT_3.

Rezultati: Povprečna vrednost razmerja pT_4/pT_3 je bila pri različnih oblikah hipertiroze statistično značilno različna ($p < 0.001$). V primerjavi z zdravimi (2.86 ± 0.52) je bila značilno višja pri HHT (3.27 ± 0.72) in ST (3.31 ± 0.54) ($p < 0.001$ za oba). Pri B je bila najnižja (2.55 ± 0.58), pri HČVJ pa najvišja (5.13 ± 1.97). Obe povprečni vrednosti sta se značilno razlikovali od vrednosti pri zdravih ($p < 0.001$) in pri bolnikih z drugimi oblikami hipertiroze ($p < 0.001$). Pri bolnikih s TA je bila povprečna vrednost razmerja pT_4/pT_3 podobna kot pri zdravih (2.85 ± 0.71) ($p = 0.085$).

Zaključki: Razmerje pT_4/pT_3 nudi koristne dodatne informacije v diagnostiki različnih oblik hipertiroze, zlasti pri B, kjer je to razmerje značilno nižje in pri HČVJ, kjer je to razmerje značilno višje kot pri drugih oblikah hipertiroze.

Abstract

Background: Different types of hyperthyroidism are treated differently. The correct diagnosis enables an adequate treatment. Clinical experience suggests that free thyroxine (fT_4) to free triiodothyronine (fT_3) ratio is different in different types of hyperthyroidism. Considering the paucity of literature data on the topic our aim was to evaluate the role of serum fT_4 to fT_3 (fT_4/fT_3) ratio in the diagnostics of various types of hyperthyroidism.

Methods: In our retrospective clinical study we included 440 consecutive subjects, examined between February and August 2010, 350 females and 90 males aged between 15 and 97 years, among them 225 healthy subjects (HS), 80 patients with Graves' disease (GD), 48 with toxic adenoma (TA), 61 patients with hyperthyroid Hashimoto's thyroiditis (HHT), 17 with subacute thyroiditis (ST), and 9 patients with iodine-induced hyperthyroidism (IIH). Thyrotropin (TSH), fT_4, fT_3 and thyroid autoantibodies were measured. The fT_4/fT_3 ratio was calculated.

Results: Mean fT_4/fT_3 ratio was significantly different for various disorders causing hyperthyroidism ($p < 0.001$). Compared with the mean fT_4/fT_3 ratio in HS (2.86 ± 0.52), the mean ratio was significantly higher in HHT and ST (3.27 ± 0.72 and 3.31 ± 0.54, respectively, $p < 0.001$ for both). In GD, the mean fT_4/fT_3 ratio was the lowest (2.55 ± 0.58) and in IIH the highest (5.13 ± 1.97). Both mean ratios significantly differed from the ratio in HS ($p < 0.001$ for both) and in other hyperthyroid patients ($p < 0.001$ for both). In patients with TA, the mean fT_4/fT_3 ratio was similar as in HS (2.85 ± 0.71) ($p = 0.085$).

Conclusion: The fT_4/fT_3 ratio offers useful additional information for the diagnostics of thyroid disorders causing hyperthyroidism, especially in GD, where this ratio is significantly lower, and in

IIH, where this ratio is significantly higher than in other types of hyperthyroidism.

Introduction

Clinical experience suggests that free thyroxine (fT_4) to free triiodothyronine (fT_3) ratio is different in different thyroid disorders. However, there is not much data on this topic in the literature. Serum fT_4/fT_3 ratio is influenced by the synthesis and secretion of thyroid hormones and by peripheral deiodination of thyroxine (T_4) to triiodothyronine (T_3) by three types of deiodinases (D1, D2 and D3).[1]

In subjects with a healthy thyroid gland, the fT_4/fT_3 ratio predominantly reflects the iodine supply and possible non-thyroidal diseases that inhibit peripheral deiodination of T_4 into T_3. It is thought that in healthy subjects, D1 activity accounts for one third and D2 activity for two thirds of daily T_3 production.[2]

In subjects with thyroid dysfunction, the synthesis and secretion of thyroid hormones changes, as does to a smaller degree the activity of deiodinases, affecting peripheral deiodination. In a hyperthyroid state, D1 activity accounts for 67 % of daily T_3 production.[2] In thyroid dysfunction, the fT_4/fT_3 ratio changes owing to differently affected thyroid function and peripheral deiodination. In patients with untreated hypothyroidism and hyperthyroidism, a higher ratio between total T_3 and T_4 than in healthy subjects or in patients with subacute thyroiditis was established.[3]

Most frequent causes of hyperthyroidism are Graves' disease (GD) and thyroid autonomy in form of toxic adenoma (TA), followed by a hyperthyroid phase of Hashimoto's thyroiditis (HHT), and subacute thyroiditis (ST). Less frequent is iodine-induced hyperthyroidism (IIH).[4] Ratio between fT_3 and fT_4 has proven to be useful for distinguishing GD from thyroiditis, but this held true only for higher fT_4 values.[5] Recent research showed different fT_3 to fT_4 ratios in different forms of GD, and a lower fT_3 to fT_4 ratio in patients treated with thyroxine because of pituitary hypothyroidism than in healthy subjects.[6,7]

To our knowledge, no data considering the ratio between fT_4 and fT_3 in various types of hyperthyroidism is available. Therefore, our aim was to evaluate the role of the fT_4/fT_3 ratio in the diagnostics of patients with various forms of hyperthyroidism. Although most studies used the fT_3/fT_4 ratio, we decided to test the fT_4/fT_3 ratio since the first ratio is usually lower than 1.0 and the second is usually higher than 1.0 thus providing more readable results and, consequently, allowing easier comparison between groups.

Subjects and methods

Study population and data collection

In our clinical retrospective study we included 440 consecutive subjects examined for the first time between February and August 2010. Since this thyroid department has had a stable catchment area of one million population for more than twenty years, the number of new cases in a certain period reflects the incidence of a certain thyroid disorder. Six thyroidologists performed a routine first examination including medical history, clinical examination, laboratory tests, thyroid ultrasound and, if necessary, thyroid scintigraphy. We included hyperthyroid patients with GD, TA, HHT, ST and IIH as well as healthy subjects (HS). All patients with GD were hyperthyroid and had an increased level of thyrotropin (TSH) receptor antibodies (TRAb). Patients with TA had subclinical (decreased TSH, normal fT_4 and fT_3) or overt hyperthyroidism (decreased TSH, increased fT_4 and/or fT_3) and were negative for TRAb. Thyroid autonomy was present on thyroid scintigraphy. Patients with HHT had subclinical or overt hyperthyroidism and an increased level of thyroid peroxidase antibodies (TPOAb) and/or thyroglobulin antibodies (TgAb). Patients with ST were subclinically or overtly hyperthyroid, had characteristic medical history and clinical status and an increased sedimentation rate. Patients with IIH were hyperthyroid and had characteristic medical

history with regard to iodine excess, which was most frequently caused by amiodarone intake. On thyroid scintigraphy, the uptake of radiopharmaceutical was diminished. HS had a normal level of TSH, fT_4, fT_3, TPOAb, TgAb, and a normal thyroid size and pattern determined by ultrasound.

The study was approved by the National Medical Ethics Committee (51/02/11).

Laboratory tests

Serum concentrations of TSH, fT_4, fT_3, TPOAb, and TgAb were measured. Additionally, TRAb was measured in patients with subclinical or overt hyperthyroidism. We calculated the fT_4/fT_3 ratio. TSH levels were measured using the ADVIA Centaur System (Siemens Medical Solutions Diagnostics, Dublin, Ireland). The reference values ranged from 0.35 to 5.5 mU/L. Levels of fT_4 and fT_3 were measured using the ADVIA Centaur System (Siemens Medical Solutions Diagnostics, Dublin, Ireland). Reference values for fT_4 and fT_3 were between 11.5 and 22.7 pmol/L and between 3.5 and 6.5 pmol/L, respectively. TPOAb and TgAb levels were measured with the ADVIA Centaur System (Siemens Medical Solutions Diagnostics, Dublin, Ireland). For TPOAb and TgAb, values above 60 KU/L were considered positive. TRAb levels were measured using RIA TRAKhuman, second generation (Brahms). Values above 1.5 U/L were considered positive.

Thyroid ultrasound

In every patient, thyroid ultrasound was performed using ALOKA machines with 7.5 MHz transducer. The size of the thyroid gland, echogenicity, and the presence of possible thyroid nodules were evaluated.

Thyroid scintigraphy

In patients with thyroid nodules and in patients with an undefined cause of hyperthyroidism, thyroid scintigraphy with technetium-99 m pertechnetate was also performed using a gamma camera with the pinhole collimator.

Statistical methods

For comparison of measured parameters between all study groups we used the ANOVA test. If the distribution was not normal (in case of TSH), we used the Kruskal Wallis test. The comparison of measured parameters between two groups was performed

Table 1: Characteristics of healthy subjects and patients with various types of hyperthyroidism. Number of all subjects in the individual group and number and percentage of females and males in each group are shown. Age of all subjects in the individual group is presented with the mean value and standard deviation.

Diagnosis	Number of subjects	Females N (%)	Males N (%)	Age (years)
HS	225	166 (73.8)	59 (26.2)	43.7 ± 19.4
GD	80	[b] 72 (90)	8 (10)	43.9 ± 14.6
TA	48	42 (87.5)	6 (12.5)	[b, d] 67.4 ± 12.5
HHT	61	[b] 58 (95.1)	3 (4.9)	[a, c, e, f] 50.7 ± 21.5
ST	17	10 (58.8)	7 (41.2)	[a, c, e, f] 53.5 ± 12.5
IIH	9	2 (22.2)	[a] 7 (77.8)	[b, d] 68.2 ± 21.3

Legend: HS, healthy subjects; GD, Graves' disease; TA, toxic adenoma; HHT, hyperthyroid Hashimoto's thyroiditis; ST, subacute thyroiditis; IIH, iodine-induced hyperthyroidism.
[a] *p < 0.05 when compared with HS*
[b] *p < 0.001 when compared with HS*
[c] *p < 0.05 when compared with GD*
[d] *p < 0.001 when compared with GD*
[e] *p < 0.001 when compared with TA*
[f] *p < 0.05 when compared with IIH*

with the Student's two-tailed t test. If the distribution was not normal (in case of TSH), the Mann Whitney U test was used instead. For comparison of the number of patients between the groups we used the χ^2 test. Statistical analysis was performed using the Statistical Package for Social Sciences software (SPSS 16.0 for Windows, SPSS Inc., Chicago, IL, USA). P value below 0.05 was considered statistically significant.

Results

Characteristics of subjects

The subjects' characteristics are presented in Table 1.

In all groups except in IIH, the percentage of women was higher than the percentage of men.

With respect to age, patients with TA and IIH were significantly older and patients with GD significantly younger compared to patients with other types of hyperthyroidism.

Laboratory results

In Table 2 we present the results of TSH, fT_4, fT_3 measurements, and of the calculated mean fT_4/fT_3 ratio in all observed groups. Groups differed significantly with respect to TSH, fT_4 and fT_3 concentration, as well as with respect to mean fT_4/fT_3 ratio ($p < 0.001$).

With regard to TSH, patients with GD presented with the lowest TSH concentration, which significantly differed from patients with TA, ST, HHT and IIH ($p < 0.001$ for all). Other groups of hyperthyroid patients did not differ with regard to TSH.

As for fT_4, patients with GD had significantly higher concentration than patients with TA, HHT and ST ($p < 0.001$, $p < 0.001$, and $p = 0.008$, respectively). However, the concentration of fT_4 was similar in patients with GD and IIH ($p = 0.100$).

Regarding fT_3, patients with GD had significantly higher concentration than patients with TA, HHT, ST and IIH ($p < 0.001$, $p < 0.001$, $p < 0.001$, and $p = 0.001$, respectively).

Accordingly, the mean fT_4/fT_3 ratio was significantly lower in patients with GD

Table 2: Mean values and standard deviations of TSH, fT4, fT3 and fT4/fT3 ratio for healthy subjects and patients with various types of hyperthyroidism. In the last row, results of the ANOVA test used for comparison of parameters between all study groups are shown as p value.

Diagnosis	TSH (mU/L)	fT_4 (pmol/L)	fT_3 (pmol/L)	fT_4/fT_3
HS	2.24 ± 1.24	14.27 ± 1.94	5.08 ± 0.68	2.86 ± 0.52
GD	[b,] 0.01 ± 0.01	[b] 37.06 ± 17.70	[b] 15.29 ± 7.62	[b, e] 2.55 ± 0.58
TA	[b, d] 0.07 ± 0.09	[b, d] 19.23 ± 6.83	[b, d] 6.95 ± 2.49	[c, e] 2.85 ± 0.71
HHT	[b, d] 0.08 ± 0.10	[b, d] 20.10 ± 5.79	[b, d] 6.38 ± 2.18	[b, d, e, f] 3.27 ± 0.72
ST	[b, d] 0.17 ± 4.11	[b, d, f] 25.02 ± 9.21	[b, d] 7.76 ± 3.50	[b, d, e, f] 3.31 ± 0.54
IIH	[b, d] 0.07 ± 0.08	[b, f] 27.02 ± 10.40	[a, c] 6.50 ± 5.76	[b, d, f] 5.13 ± 1.79
P value	<0.001	<0.001	<0.001	<0.001

Legend: HS, healthy subjects; GD, Graves' disease; TA, toxic adenoma; HHT, hyperthyroid Hashimoto's thyroiditis; ST, subacute thyroiditis; IIH, iodine-induced hyperthyroidism; TSH, thyrotropin (reference value 0.35–5.5 mU/L); fT4, free thyroxine (reference value 11.5–22.7 pmol/L); fT3, free triiodothyronine (reference value 3.5–6.5 pmol/L).

[a,] *p < 0.05 when compared with HS*
[b,] *p < 0.001 when compared with HS*
[c,] *p < 0.05 when compared with GD*
[d,] *p < 0.001 when compared with GD*
[e,] *p < 0.001 when compared with IIH*
[f,] *p < 0.05 when compared with TA*

than in patients with TA, HHT, ST and IIH ($p = 0.011$, $p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively). In patients with IIH, the mean fT_4/fT_3 ratio was the highest and differed significantly from the mean fT_4/fT_3 ratio in all other groups of hyperthyroid patients ($p < 0.001$ for all). In patients with TA, the mean fT_4/fT_3 ratio was significantly lower than in patients with HHT and ST ($p = 0.003$, $p = 0.018$, respectively). However, in patients with HHT, the mean fT_4/fT_3 ratio was similar as in patient with ST ($p = 0.829$). As compared with HS, the mean fT_4/fT_3 ratio was significantly lower in patients with GD ($p < 0.001$), similar in patients with TA ($p = 0.085$), and significantly higher in patients with HHT, ST and IIH ($p < 0.001$ for all).

As shown in Table 3, the highest sensitivity and specificity of the fT_4/fT_3 ratio for the classification into the correct diagnostic group was for GD and TA below 3.0, for HHT and ST above 3.0, and for IID above 4.0. However, in GD and TA, 17/80 (21.3 %) and 18/48 (37.5 %) patients, respectively, had this ratio above 3.0. In HHT and ST, 26/61 (42.6 %) and 2/17 (11.8 %) patients, respectively, had this ratio below 3.0. In IID, 2/9 (22.2 %) patients had this ratio below 4.0.

Discussion

Our results indicate the useful role of fT_4/fT_3 ratio in the diagnostics of hyperthyroidism. In different disorders causing hyperthyroidism, the mean fT_4/fT_3 ratio is significantly different–the lowest in patients with GD and the highest in patients with IIH. Although our results cannot provide precise cut-off values of fT_4/fT_3 ratios for the differentiation between various types of hyperthyroidism, the present findings may serve as a valuable and simple additional diagnostic instrument.

The proportion of subjects in different groups in a defined observation period is in accordance with the known incidence of thyroid diseases in Slovenia.[8] From the present study and from an earlier one we may conclude that in the iodine-sufficient area of Slovenia the most frequent thyroid disorder causing hyperthyroidism is GD.[8]

When comparing the gender and age distribution of our patients between different groups, the characteristics are consistent with the epidemiological data from the literature. Women are more often affected by thyroid disorders than men, especially by autoimmune thyroid disorders such as GD and HHT.[9,10] Only IIH is more prevalent in men, most likely because of more frequent use of amiodarone in male population.[11,12]

As for age, patients with TA and IIH were significantly older than patients with other types of hyperthyroidism. In TA, this is probably the consequence of slowly developing hyperthyroidism in autonomous tissue.[4] It was established that one out of five patients with TA with a diameter of 3 cm and more developed hyperthyroidism within 1 to 6 years.[13] In IIH, the most plausible explanation is a combination of more frequent use of amiodarone in older patients and a higher incidence of preexisting TA.[14]

Various types of hyperthyroidism differed with respect to the severity of hyperthyroidism reflected in the level of fT_4 and fT_3, which was the highest in patients with GD. However, the differences in the severity of hyperthyroidism among different types of hyperthyroidism were not as significant as the differences in the calculated mean fT_4/fT_3 ratio. This can be explained by the changing role of deiodinases in hyperthyroidism. It was shown that in hyperthyroidism the effect of D2 decreases because fT_4 and fT_3 inhibit its synthesis and activity.[2,15] Additionally, a higher fT_3 concentration increases transcription and activity of D1 which has the main role in hyperthyroidism being responsible for approximately 70 % of produced T_3.[16,17] D1 converts about 50 % of T_4 into T_3 and remaining 50 % of T_4 into reverse T_3 without biological potential. Therefore, D1 is less effective in this conversion than D2, which converts 100 % of T_4 into T_3. A combination of weak D1 efficacy, high D1 expression and differently increased synthesis of both thyroid hormones varies with the type and severity of hyperthyroidism and therefore significantly influences the fT_4/fT_3 ratio.

In GD, most patients had the fT_4/fT_3 ratio below 3.0. Different factors are responsible for a significantly lower calculated mean

fT_4/fT_3 ratio than in other disorders causing hyperthyroidism, and for a lower ratio than even in HS. In thyroid gland of GD patients, the synthesis of thyroid hormones is intense owing to the influence of TRAb. In GD, relatively more T_3 than T_4 is produced than in HS.[17] The reason could be that the thyroid gland in GD patients contains less iodine than the thyroid gland of HS as has been proven by intrathyroidal measurement of iodine content in different thyroid disorders.[18] It was shown that lower intrathyroidal iodine content changes the equilibrium of thyroid hormone synthesis from prevailingly T_4 production to T_3 production.[19] Additionally, in the thyroid gland of GD patients, the increased activity of both D1 and D2 was established.[6] In the periphery, a high fT_3 serum concentration stimulates the activity of D1 and inhibits the activity of D2. Most likely, a combination of all listed factors leads to importantly lower mean fT_4/fT_3 ratio in GD than in other disorders causing hyperthyroidism.

In HHT and ST, most patients had the fT_4/fT_3 ratio above 3.0. As indicated in our own and in previous studies, destructive disorders causing hyperthyroidism, such as ST and HHT, present a higher fT_4/fT_3 ratio than GD.[3,5,20] However, in the present study, the calculated mean fT_4/fT_3 ratio was higher in HHT and ST than in HS, which is not in line with previous findings of similar ratios between these groups.[3] In HHT and ST, the destruction of thyroid cells leads to thyroid hormone release with consequent hyperthyroidism. It is known that in the euthyroid thyroid gland, T_4 is mostly produced. After destruction, predominantly fT_4 is released, which presumably contributes to the higher fT_4/fT_3 ratio.

In IIH, the reasons for a distinctively higher calculated mean fT_4/fT_3 ratio in comparison with other types of hyperthyroidism are various. Most patients had the fT_4/fT_3 ratio above 4.0. Amiodarone with its high iodine content increases the synthesis of T_4 and to a lesser extent of T_3. This happens most frequently in patients with thyroid autonomy, known to be incapable of autoregulation.[21] Moreover, amiodarone decreases peripheral conversion of T_4 into T_3 by inhibition of deiodinases and may act cytotoxically on thyroid cells, and therefore additionally contributes to a higher fT_4/fT_3 ratio.[22]

A limitation of our retrospective study is a different number of patients with various disorders causing hyperthyroidism in the observed period, especially the low number of patients with IIH, which is a rare cause of hyperthyroidism. However, in spite of the low number, the mean fT_4/fT_3 ratio in IIH was significantly higher compared to other types of hyperthyroidism.

In conclusion, the calculated fT_4/fT_3 ratio offers useful additional information for the diagnostics of thyroid disorders causing hyperthyroidism. While in GD the mean fT_4/fT_3 ratio is significantly lower, in IIH the mean fT_4/fT_3 ratio is significantly higher than in other types of hyperthyroidism. However, this ratio should be used cautiously and only as an additional information along with other well-established diagnostic criteria which enable differentiation between various types of hyperthyroidism.

Table 3: Sensitivity and specificity of a certain fT4/fT3 ratio for the classification of hyperthyroid patients into correct group.

Parameter	GD (fT_4/fT_3 below 3.0) (95 % CI)	TA (fT_4/fT_3 below 3.0) (95 % CI)	HHT (fT_4/fT_3 above 3.0) (95 % CI)	ST (fT_4/fT_3 above 3.0) (95 % CI)	IIH (fT_4/fT_3 above 4.0) (95 % CI)
Sensitivity	78.8 % (68.2–87.1 %)	62.5 % 47.3–76.0 %	57.4 % 44.1–67 %	88.2 % 63.5–98.2 %	77.8 % 40.1–96.5 %
Specificity	55.6 % 46.8–64.3 %	44.9.2 % 37.2–52.8 %	62.3 % 54.2–70.0 %	60.6 % 53.4–67.5 %	93.2 % 88.9–96.2 %

Legend: GD, Graves' disease; TA, toxic adenoma; HHT, hyperthyroid Hashimoto's thyroiditis; ST, subacute thyroiditis; IIH, iodine-induced hyperthyroidism; CI, confidence interval.

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