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Research Article

The Impact of Serum Triiodothyronine to Thyroxine (T3/T4) Ratio in Euthyroid Subjects

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Abstract

Background: The T3/T4 ratio is an index which reflects thyroid function and the action of hormones on the tissues.

Methods: A total of 140 euthyroid subjects were enrolled in this study and classified into two groups. Group A (n =100) had normal values of thyroid hormones and negative values of antibodies, i.e. TPO-Ab < 34U/L and TgAb < 115 U/L. Group B (n =40) had normal values of thyroid hormones and positive antibody, i.e. TPO-Ab > 34U/L and /or TgAb > 115 U/L.

Serum thyroid hormones and antibodies concentration was measured by electrochemiluminescence immunoassay (ECLIA, Roche Diagnostics, Mannheim, Germany).

Results: Serum levels thyroid parameters of group A vs. group B were: T3/T4 ratio, mean 0.0168 *vs*. mean 0.0153 (p<0.001); T3 (nmol/L), median 1.61vs. median 1.49 (p=0.009) and T4 (nmol/L) median 96.46 *vs*. median 100.73 (p=0.203). In both groups, there were correlations of the T3/ T4 ratio with thyroid hormones. In the group A, the T3 positively correlated with T4 (r = 0.504; p < 0.001) and fT3 with fT4 (r =0.318; p < 0.001) but in the group B the T3 positively correlated with T4 (r = 0.545; p = 0.004) while fT3 was not correlated with fT4 (r = 0.178; p = 0.385).

Conclusion: Euthyroid subjects with positive thyroid antibodies have less value of T3/T4 ratio than subjects with negative antibodies, as well as value of T3. This finding may point to a decreased ability of tissue T4 5'-deiodination.

Keywords: Triiodothyronine; Triiodothyronine to thyroxine ratio; Thyroid peroxidise antibodies

Abbreviations

TSH: Thyroid Stimulating Hormone; T4: Thyroxine; fT4: Free Thyroxine; T3: Triiodothyronine; fT3: Free T3; TPO-Ab: Thyroid Peroxidise Antibodies; Tg-Ab: Thyroglobulin Antibodies; Tg: Thyroglobulin

Introduction

The thyroid gland synthesizes Thyroxine (T4) and Triiodothyronine (T3) that act on nearly every cell in the body and both of these hormones intensely increase the metabolic rate of the body. Thyroid hormones are metabolized in peripherial tissues and alterations in these metabolic transformations might significantly impact on their biologic potency and regulate their biologic effects. In normal humans about 90% of hormone released from the thyroid gland. Triiodothyronine is also released from the thyroid but approximately 80% is derived from the peripheral tissues by the enzymatic removal of a single 5′ iodine atom (outer ring or 5′ monodeiodination) from T_4 [1]. T3 represents the active form of thyroid hormones; it increases cardiac output, cardiac contractility and heart rate and decreases systemic vascular resistance [2].

Thyroid Peroxidase (TPO) is a key enzyme in the formation of thyroid hormones and a major auto antigen in autoimmune thyroid diseases [3]. Anti-Thyroid Peroxidise Antibodies (TPO-Ab) are very important to diagnose autoimmune thyroid diseases and likewise in estimating its clinical course [4]. Likewise, the TPO-Ab correlate with the degree of lymphocytic infiltration in euthyroid subjects, and they are often present in euthyroid subjects (prevalence 12-26%) [3].

Today, the initial screening for suspected hypothyroidism is Thyroid Stimulating Hormone (TSH). For screening usually alone TSH will suffice. In practice, when TSH is abnormal, laboratories provide added the measurement of free T4, instead of a repeat venipuncture on another occasion. A normal TSH indicates euthyroidism and further testing is not required. Thyroid antibodies (thyroid peroxidase and thyroglobulin) may be used in at-risk subjects to stratify for future thyroid dysfunction. Measuring TPO antibodies in euthyroid subjects can be used to identify subjects with increased risk for hypothyroidism. Routine of thyroid function tests screen in an asymptomatic subject is controversial [5] though this was proposed by the American Thyroid Association in 2000 [6]. Recently, the USPSTF focuses on nonpregnant, asymptomatic adults and concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for thyroid dysfunction [7]. Also, some studies have not found evidence on benefits and harms of screening versus not screening [8].

The T3/T4 ratio is an index which reflects thyroid function and the action of hormones on the tissues. It is a very useful aid for the

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diagnosis of borderline thyrotoxicosis, euthyroid sick syndrome [9], replacement therapy, the action of different drugs on thyroid function and/or hormone levels as well as iodine deficiency [10]. Likewise, T3/T4 ratio has a prognostic value for the relapse of hyperthyroidism in post-treated hyperthyroid patients [11] and can distinguish a typical hyperthyroidism from destructive thyroiditis [12].

The aim of this study was to examine the T3/T4 ratio in euthyroid subjects with positive antibodies (antibodies for TPO or thyroglobulin or both antibodies) compared with T3/T4 ratio of euthyroid subjects with negative antibodies and to examine the significance of this relationship.

Materials and Methods

A total of 140 euthyroid subjects were enrolled in this study and classified into two groups. Group A (n =100) had normal values of thyroid hormones and negative values of antibodies, i.e. TPO-Ab < 34U/L and TgAb < 115 U/L. Group B (n =40) had normal values of thyroid hormones and positive antibody, i.e. TPO-Ab > 34U/L and / or TgAb > 115 U/L.

Subjects were voluntarily included in the study at the Health Centre Laktasi and the Clinical Centre of Banja Luka. The study was approved by the National Ethics Committee. Written consent was obtained from participating subjects. Subjects with medicament of thyroid diseases as well as medications known to affect the hypothalamic-pituitary-thyroid axis (amiodarone, glucocorticoids) and also subjects with a positive history of thyroid diseases were excluded. For the thyroid hormones and antibodies measurement, blood samples were taken in the morning, between 7:00 and 10:00 a.m., after 12–14 h of fasting.

Serum thyroid hormones and antibodies concentration was measured by electrochemiluminescence immunoassay (ECLIA, Roche Diagnostics, and Mannheim, Germany). The reference range for the TSH assay was 0.27 to 4.2 mIU/L, and the functional sensitivity provided by the manufacturer was 0.014 mIU/L. Expected values for euthyroid subjects were**:** 66-181 nmol/L of T4; 12-22 pmol/L of fT4; 1.3-3.1 nmol/L of T3; 3.1-6.8 pmol/L of fT3; borderline value of 34 IU/mL of TPO-Ab and threshold value of 115 IU/mL of Tg-Ab. Reliability of the measurement results was regularly checked through assessment of appropriate controls and application of the internal and the external quality control principle.

All calculations were performed using SPSS v.20.0 (SPSS Inc., Chicago, IL, USA). Numerical data were expressed as the mean and 95% confidence interval for the mean (CI) or median and Interquartile Range (IQR). The Kolmogorov–Smirnov test was used to test normality. Comparisons of the data were performed by the Student's t test for normally distributed and Wilcoxon's signed rank test for non-normally distributed. The correlation between the values of samples was determined by Pearson correlation test or the Spearman rank-order correlation test.

Results and Discussion

Subjects were divided in two groups according to thyroid antibodies. Subjects in the group A (n =100) had normal values of thyroid hormones and negative values of antibodies, while in the group B (n = 40) subjects had normal values of thyroid hormones and positive antibody.

Table 1: Laboratory characteristics of the euthyroid subjects.

Parametar	Group A (n=100)	Group B (n=40)	p
TSH (mIU/L)	1.93 (1.38; 2.72)[a]	2.13 (1.78; 3.87)[a]	0.116
T4 (nmol/L)	96.46 (87.63; 107.60)[a]	100.73 (90.67;113.20)[a]	0.203
fT4 (pmol/L)	16.32 (16.04;16.59)[b]	16.24 (15.55;16.93)[b]	0.642
T3 (nmol/L)	1.61 (1.44;1.85)[a]	1.49 (1.40;1.76)[a]	0.009
fT3 (pmol/L)	5.26 (5.18;5.34)[b]	5.0 (4.79;5.20)[b]	0.07
T3/T4	0.0168(0.0164;0.0172)[b]	0.0153(0.0144;0.0162)[b]	<0.001

Group A had negative values of thyroid antibodies, Group B had positive values of thyroid antibodies; [a]Data are presented as median (IQR); [b]Data are presented as mean (95%CI).

There were no differences between the two analyzed groups in terms of age, body mass index but there was in terms of gender (group B comprised of 80% females) (results not shown).

Values of thyroid hormones are shown in Table 1. In both groups there were correlations of the T3/ T4 ratio with thyroid hormones (results not shown). In group A the T3 positively correlated with T4 ($r = 0.504$; $p < 0.001$) and fT3 with fT4 ($r = 0.318$; $p < 0.001$) but in the group B the T3 positively correlated with T4 ($r = 0.545$; $p = 0.004$) while not correlated fT3 with fT4 ($r = 0.178$; $p = 0.385$).

Our study indicates that euthyroid subjects with positive antibodies had lower values of T3/T4 ratio than subjects with negative antibodies. Likewise, they had lower values of T3 hormones which were in the range of reference values.

Results of some studies indicated that the T3/T4 ratio is an index reflecting thyroid function and the action of hormones on the tissues [13]. Due to the higher secretion of T3, T3/T4 ratio is increased in hyperthyroidism, but also it is increased 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 [13]. However, in hypothyroidism T3/T4 ratio is much higher because of the decline of T4 levels.

Thyroid antibodies, i.e. Anti-Thyroid Peroxidise Antibodies (TPO-Ab) and Anti-Thyroglobulin Antibodies (Tg-Ab), have been used to aid in the differential diagnosis of thyroid disorders. The study US NHANES III showed that Tg-Ab was positive in 10.4% and TPO-Ab in 11.3% of thyroid disease-free subjects [14]. TPO-Ab was significantly associated with hypo or hyperthyroidism, but TgAb was not associated with abovementioned. Also, TPO-Ab has sufficient specificity and sensitivity to be used singly for diagnosis of autoimmune thyroditis [15]. The results of our study indicate that T3/T4 ratio could be an additional parameter in the early recognition of future events, i.e. hypo or hyperthyroidism of thyroid disease-free subjects. A significant decrease in the value of T3 in this group may be a consequence of modified entry of thyroid hormone into tissue as well as changes in thyroid hormone metabolism due to change expression of the deiodinases or the decreased 5'-deiodinase tissue's activity. In additionally, the significantly lower T3 levels in this group of subjects justify the newer approaches of combined therapies, i.e. Thyroxine (T_4)/Triiodothyronine (T_3) combination therapy, because some patients are not able to benefit from monotherapy due to defects in their deiodinase enzymes converting Thyroxine (T_4) to T_3 [16]. Today, the standard treatment of hypothyroidism is only consisted of Thyroxine (T4) administration.

Absence of the expected correlation of fT3 with fT4 in the subjects

with positive thyroid antibody may point to the altered binding of thyroid hormone to carrier proteins. The clinical significance of this finding should be further investigated. Our study design indicates that T3/T4 ratio may be parameter for differential of thyroid homeostasis or tool of clinical research.

Conclusion

Euthyroid subjects with positive thyroid antibodies have less value of T3/T4 ratio than subjects with negative antibodies, as well as value of T3. This finding may point to a decreased ability of tissue T4 5'-deiodination.

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