







CHANGES OF TSH, FT3 AND FT4 LEVELS IN PATIENTS WITH HYPERTHYROIDISM

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ABSTRACT

Introduction: The thyroid hormone secretion disorders may be hyperthyroidism (reduced TSH levels and increased levels of FT3 and FT4) and subclinical hyperthyroidism (decreased concentration of TSH with normal FT3 and FT4).

Aim: To investigate levels of thyroid hormones (TSH, FT3, and FT4) in patients with hyperthyroidism or subclinical hyperthyroidism treated at Tuzla Blue Clinic.

Materials and methods: The study included 120 patients divided into three groups: a control group, groups with respondents who have hyperthyroidism, and a group of patients with subclinical hyperthyroidism. The concentrations of the hormones TSH, FT3, and FT4 were analyzed. The determination was carried out on the device IMMULITE 1 Siemens using the immunochemistry method.

Results: TSH between our group investigated the existence of significant statistical differences between the control group and the group with hyperthyroidism ($p < 0.0001$) and between the control group and the group with subclinical hyperthyroidism ($p = 0.0001$), and the parameter FT3 showed that a statistically significant difference exists between the control group and the group with hyperthyroidism ($p < 0.0001$), and between patients with hyperthyroidism and subclinical hyperthyroidism ($p < 0.0001$). For FT4, we found a statistically significant difference between the control group and the group with

hyperthyroidism ($p < 0.0001$) and between groups with hyperthyroidism and subclinical hyperthyroidism ($p < 0.0001$).

Conclusions: The concentration of TSH is reduced in both hyperthyroidism and subclinical hyperthyroidism. The serum concentrations of FT3 and FT4 are elevated in hyperthyroidism, while in subclinical hyperthyroidism, the serum concentrations of FT3 and FT4 stand in the reference area.

Keywords: Thyrotropin, thyroxine, TSH, FT3, FT4, hyperthyroidism

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INTRODUCTION

In routine clinical practice, thyroid dysfunction is very common. During life, the prevalence of thyroid dysfunction is approximately 5–10% (1). One of the roles of thyroid-stimulating hormone (TSH) is regulation of the synthesis and secretion of the thyroid hormone (2) and is considered the primary indicator to assess thyroid function (3). According to the American Thyroid Association (ATA), for laboratory testing of thyroid function, it is recommended to use thyrotropin (TSH), free thyroxine (FT4), or FT4 combined with total triiodothyronine (TT3). The importance of determining TSH activity includes: primary hypothyroidism and hyperthyroidism; secondary hypothyroidism (with determination of free T4); control of the treatment; pregnant women's euthyroidism; and states of latent hyperthyroidism (e.g., toxic thyroid adenoma) (4). In the blood, T4

concentration depends on synthesis and secretion from the thyroid and utilization in peripheral tissues. The FT4 concentration reflects the synthesis and secretion of T4, the conversion of T4 into T3, and the elimination of hormones. One of the main roles of T4 is its conversion to T3 by deiodination via the enzyme deiodinase I (1, 5). Pearce et al. makes a definition of subclinical thyrotoxicosis (SCT), or subclinical hyperthyroidism, as a biochemical state in which the serum thyroid stimulating hormone (TSH) is below the reference range but with normal concentrations of circulating free thyroid hormones (FT4, FT3). The main differences are in etiology and outcome depending upon whether the serum TSH is in the low but detectable range (0.1–0.4 mIU/l) or fully suppressed (< 0.1 mIU/l). According to the investigation of Pearce et al. and Garber, patients with SCT and a fully suppressed

TSH do have mild thyroid autonomy or early thyrotoxicosis, although the rate of progression to overt hyperthyroidism is low, at only 3-5% annually. Common causes of subclinical hyperthyroidism include excessive levothyroxine replacement, autonomously functioning multi-nodular goiter, and subclinical Graves' disease. One of the potentially risky factors for these patients is developing atrial fibrillation and possibly osteoporosis (6, 7).

The aim of our study was to investigate levels of thyroid hormones (TSH, FT3, and FT4) in patients with hyperthyroidism or subclinical hyperthyroidism treated at Tuzla Blue Clinic.

MATERIAL AND METHODS

The retrospective study was conducted in the Blue Polyclinic, Tuzla, and included data from medical records collected from the beginning of 2018 to the end of 2019. The study included 120 patients aged over 50 who were divided into three groups: patients with hyperthyroidism, patients with subclinical hyperthyroidism, and a control group. The inclusion criteria were patients with hyperthyroidism or subclinical hyperthyroidism before the introduction of therapy. The exclusion criteria were patients with diabetes

mellitus, patients with other hormonal imbalances, and patients undergoing therapy for the treatment of hyperthyroidism or subclinical hyperthyroidism.

The determination of TSH, FT3, and FT4 hormones was performed on the IMMULITE 1 immunochemical analyzer, which is based on the immunochemical method. The principle of the immunochemical method in this case is the chemiluminescence reaction. The method is based on the binding of antigens from serum and antibodies from reagents labeled with alkaline phosphatase. The method is based on two binding sites, i.e., "sandwich" immunoassay, where chemiluminescence is used for detection. First, a conjugate of alkaline phosphatase (reagent) is formed with paramagnetic particles (which serve as a solid substrate to which monoclonal antibodies are attached) during the immune reaction. In this way, monoclonal antibodies are labeled with alkaline phosphatase. The alkaline phosphatase that binds to the granules (solid plates) dephosphorylates the substrate (adamantyl dioxyethane phosphate) into an unstable anion intermediate. The unstable intermediate emits light after decay. The amount of light

emitted is directly proportional to the amount of alkaline phosphatase bound (8).

STATISTICAL ANALYSIS

The software packages used for data processing were Statistical Package for Social Sciences (SPSS) version 21.0 and MedCalc. The data obtained are presented in tables and figures. In order to establish the existence of a statistically significant difference in the examined parameters (TSH, FT3, FT4), between the groups of subjects, we used the Mann Whitney U test, in which we performed a statistical examination of two groups against each other, that is, their cross-examination "each with each." Based on this test, statistically significant differences between individual groups of respondents and the individual examined parameters are analyzed in detail.

Microsoft Excel for Windows was used to prepare and store the data for statistical analysis. The Qi Macros 2019 program was used for the graphical layout. The tested results were statistically processed for $p < 0.001$.

RESULTS

In order to establish the existence of a statistically significant difference in the examined parameters (TSH, FT3, FT4),

between the groups of subjects, we used the Mann Whitney U test $p < 0.001$, in which we performed a statistical examination of two groups against each other, that is, their cross-examination "each with each." Based on this test, statistically significant differences between individual groups of respondents and the individual examined parameters are analyzed in detail.

In a group of patients with hyperthyroidism, the TSH value was 0.016 mIU/L, for FT3 11,96 pg/mL, and for FT4 51,32 pmol/L. The standard deviation for TSH is 0.028 mIU/L, for FT3 it is 4.94 pg/mL, while for FT4 it is 15.43 pmol/L, which indicates that FT4 also has the highest dispersion of results in this case, in the case of hyperthyroidism. The minimum value for TSH was 0.004 mIU/L, for FT3 6.80 pg/mL, and for FT4 24.50 pmol/L, while the maximum value for TSH was about 13 mIU/L, for FT3 26.90 pg/mL, and for FT4 77.20 pmol/L.

The second group has subclinical hyperthyroidism. The mean value for TSH was 0.088 mIU/L, for FT3 3.77 pg/mL, and for FT4 17.27 pmol/L. The standard deviation for TSH is 0.081 mIU/L, for FT3 it is 0.78 pmol/L, while for FT4 it is 3.38 pmol/L, where FT4 again has the highest dispersion of results. The minimum value

for TSH was 0.004 mIU/L, for FT3 2.4 pg/mL, and for FT4 11.6 pmol/L, while the maximum value for TSH was 0.26 mIU/L, for FT3 5.6 pg/mL, and for FT4 22.9 pmol/L. In the control group, the mean value for TSH was 1.5 mIU/L, for FT3 3.41 pg/mL, and for FT4 14.83 pmol/L. The standard deviation for TSH is 0.587 mIU/L, for FT3 it is 0.612 pmol/L, and for FT4 it is 1.52 pmol/L, which indicates that FT4 has the highest dispersion of results. The minimum value for TSH was 0.63 mIU/L, for FT3 2.3 pg/mL, and for FT4 12.3 pmol/L, while the maximum value for

TSH was 2.7 mIU/L, for FT3 4.6 pg/mL, and for FT4 18.2 pmol/L.

Based on the mean values of the tested parameters TSH, FT3, and FT4 between the three groups of subjects, we can observe the significance and connection of the parameters, as well as the differences between individual groups of subjects. In Figures 1, 2, and 3, the average concentrations of TSH, FT3, and FT4 in the investigation groups are shown: TSH (Figure 1), FT3 (Figure 2), and FT4 (Figure 3).

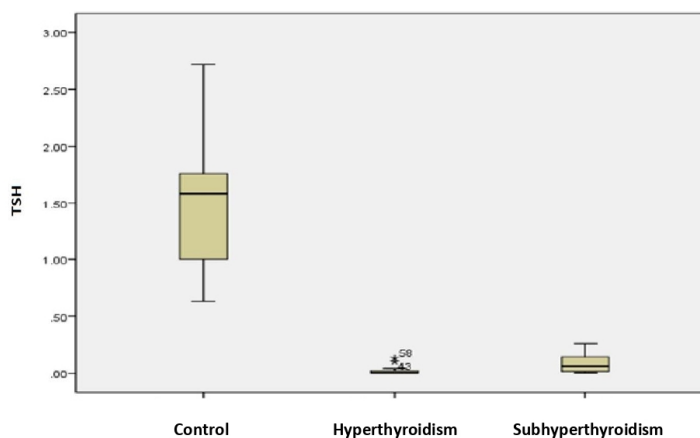


Figure 1. - The average TSH values in three groups of subjects

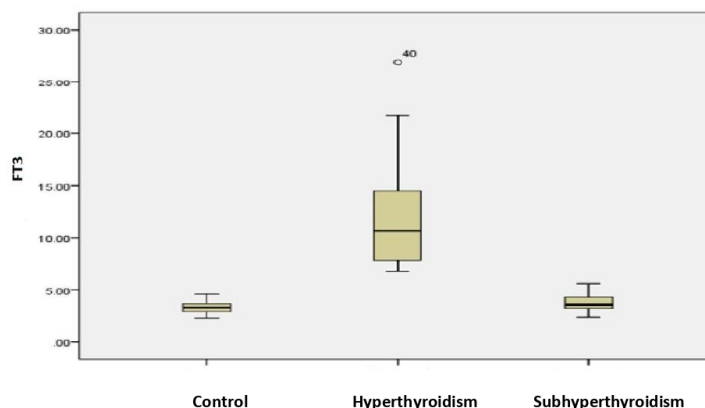


Figure 2. - The average FT3 values in three groups of subjects

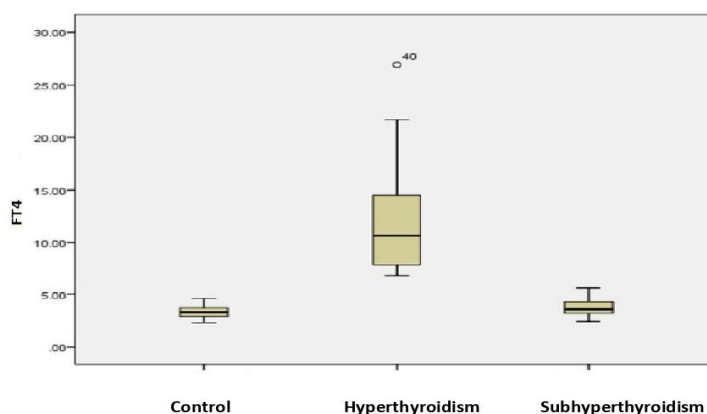


Figure 3. - The average FT4 values in three groups of subjects

If we look at our reference values for all three parameters measured on the IMMULITE 1 device, TSH (0.4–4.0 mIU/L); FT3 (2.3–6.4 pg/mL), and FT4 (10.3–24.3 pmol/L), we see that the values for TSH in the control group are around 1.5 mIU/L, while the values in the group of subjects with hyperthyroidism and subclinical hyperthyroidism are significantly below the lower reference limits, in contrast to the already mentioned TSH value for the control group, which is within the reference values. In the values

for FT3, we see a return of the same value within normal limits in the control group of subjects and the group with subclinical hyperthyroidism, and a deviation in the value in the group with hyperthyroidism. The same case can be applied to the FT4 value, which is within the reference range in the control group and in subjects with subclinical hyperthyroidism, while we observe a deviation in the group with hyperthyroidism.

The Man Whitney's U test showed that the value of parameter TSH between our group

investigated the existence of significant statistical differences between the control group and the group with hyperthyroidism ($Z = 6.743$; $p < 0.0001$) and between the control group and the group with subclinical hyperthyroidism ($Z = 6.654$; p

$= 0.0001$). Using the same test in groups with hyperthyroidism and subclinical hyperthyroidism, we got significant statistical differences ($Z = 4.314$; $p < 0.0001$), as shown in Table 1.

Table 1. - Comparison of serum TSH concentrations between the studied groups

| Comparison groups | Mann-Whitney U | Z | P |
|---|----------------|-------|----------|
| TSH Hyperthyroidism /Control group | <0.001 | 6.743 | <0.0001* |
| TSH Subclinical hyperthyroidism/ control group | <0.001 | 6.654 | 0.0001* |
| TSH Hyperthyroidism / Subclinical hyperthyroidism | 165 | 4.314 | <0.0001* |

For FT4, we found a statistically significant difference between the control group and the group with hyperthyroidism ($Z = 6.621$; $p < 0.0001$) and between groups with hyperthyroidism and subclinical hyperthyroidism ($Z = 6.653$; p

< 0.0001). Using the same test in the group with subclinical hyperthyroidism and the control group, we got significant statistical differences ($Z = 2.484$; $p = 0.013$), as shown in Table 2.

Table 2. - Comparison of serum FT4 concentrations between the studied groups

| Comparison groups | Mann-Whitney U | Z | P |
|---|----------------|-------|----------|
| FT4 Hyperthyroidism /Control group | 30 | 6.621 | <0.0001* |
| FT4 Subclinical hyperthyroidism/ control group | 282 | 2.484 | 0.013 |
| FT4 Hyperthyroidism / Subclinical hyperthyroidism | <0.001 | 6.653 | <0.0001* |

In our study, there was a significant difference between concentrations of FT3

between the control group and the group with hyperthyroidism ($Z = 6.654$; p

<0.0001) and between groups with hyperthyroidism and subclinical hyperthyroidism ($Z = 6.655$; $p < 0.0001$). We got a **difference** between

concentrations of FT3 subclinical hyperthyroidism and the control group ($Z = 1.746$; $p = 0.080$), as shown in Table 3.

Table 3. - Comparison of serum FT3 concentrations between the studied groups

| Comparison groups | Mann-Whitney U | Z | P |
|--|----------------|-------|----------|
| FT3 Hyperthyroidism /Control group | <0.001 | 6.654 | <0.0001* |
| FT3 Subclinical hyperthyroidism/ control group | 332 | 1.746 | 0.080 |
| FT3 Hyperthyroidism / Subclinical hyperthyroidism | <0.001 | 6.655 | <0.0001* |

DISCUSSION

Our research was aimed at determining a decrease in the concentration of TSH hormone with a simultaneous increase in the concentration of FT3 and FT4 hormones in hyperthyroidism, and a decrease in the concentration of TSH hormone with normal concentrations of FT3 and FT4 in subclinical hyperthyroidism. Also, one of the goals was to compare the obtained concentrations of TSH, FT3, and FT4 between the groups of subjects in order to determine the difference between hyperthyroidism and subclinical hyperthyroidism.

The determination of the TSH mean value, which is used to measure thyroid dysfunction, has been associated with the

development of hyperthyroidism. The lowest value of TSH serum concentration was found in the group with hyperthyroidism; the mean value was 0.016 mIU/L, compared to the group with subclinical hyperthyroidism. The mean value for TSH was 0.088 mIU/L, while the subjects in the control group had a mean value of 1.5 mIU/L. The maximum value for the TSH parameter was measured in the control group of patients and is 2.72 mIU/L. The minimum value measured for TSH in the group with hyperthyroidism was 0.004 mIU/L (Figure 1).

For the parameter FT3, the highest mean concentration of 11.96 pg/mL was found in the group with hyperthyroidism and subclinical hyperthyroidism (3.77 pg/mL), and the control group's FT3 concentration

was 33.41 pg/mL. The maximum value for FT3 (26.90 pg/mL) was measured in the group of subjects with hyperthyroidism, while the minimum value for the FT3 parameter was measured in the control group of subjects (2.30 pg/mL) (Figure 2.). The highest mean values of the FT4 parameter were found in the hyperthyroid group at 51.32 pmol/L, in the subclinical hyperthyroidism group at 17.27 pmol/L, and in the control group at 14.83 pmol/L. The minimum value for FT4 was measured in the group of subjects with subclinical hyperthyroidism and was 11.6 pmol/mL (Figure 3.).

The study from Hoogendoorn EH found that 3.9% of patients in the study 3.9% were diagnosed with subclinical hyperthyroidism, with a TSH concentration < 0.1 mIU/l, while 0.2 were diagnosed with hyperthyroidism, the rest of the subjects were a group of euthyroid patients (9). In another study from the USA in which 968 subjects participated, 2.5% of US residents had a TSH concentration < 0.1 mIU/l, that is, they belonged to the group of subclinical hyperthyroid patients (10, 11). In the investigation in the Germany area with iodine deficiency, respondents without previously known thyroid disease, had a concentration of TSH < 0.1 mIU/l and normal

concentrations of FT3 and FT4, which concluded that it was a subclinical hyperthyroidism (12). The study by Favresse J. found that subjects with overt hyperthyroidism will have low or suppressed TSH levels with elevated free T4 and total T3 levels. Patients with mild/subclinical hyperthyroidism will have low or suppressed TSH with normal free T4 and total T3 levels. 'T3 toxicosis' is defined as low/suppressed TSH with normal T4 and elevated T3 levels (13). Generally, serum FT3 is predominantly elevated in endogenous subclinical hyperthyroidism, such as Graves' disease, resulting in a high FT3/FT4 ratio (14).

By measuring the value of TSH between our examined groups, we found that there is a significant statistical difference both between the control group and the group with hyperthyroidism ($p < 0.0001$) and between the control group and the group with subclinical hyperthyroidism ($p = 0.0001$), and for the parameter FT3, a statistically significant difference exists between the control group and the group with hyperthyroidism ($p < 0.0001$), and between subjects with hyperthyroidism and those with subclinical hyperthyroidism ($p < 0.0001$). For FT4, we got a statistically significant difference between the control group and the group with hyperthyroidism

($p < 0.0001$) and between the group with hyperthyroidism and subclinical hyperthyroidism ($p < 0.0001$). The results for FT3 and FT4 in the group with subclinical hyperthyroidism and the control group showed no statistically significant difference ($p < 0.001$), as shown in Tables 1–3.

Overt hyperthyroidism affects 1.9% of women and 0.16% of men and is characterized by a TSH level lower than the reference range and FT4 and/or FT3 levels above the normal reference range. Complications include Graves' ophthalmopathy, thyrotoxic crisis, atrial fibrillation, loss of bone mass, and congestive heart failure (15). The study of Gan et al. shows that there is evidence to support an association between cognitive impairment and subclinical hyperthyroidism or low TSH within the reference range (16). The female patients in study conducted by Tan who had TSH levels in the lowest tertile (less than 1 mIU per L) had a higher risk of Alzheimer disease (HR = 2.39; 95% CI, 1.47 to 3.87) over a mean 12.7-year follow-up period compared with those whose TSH levels were in the middle tertile (17). Results of Canaris et al. have found that subclinical hyperthyroidism is most common in patients receiving thyroid hormone

replacement therapy; the prevalence in these patients may be as high as 20% (18), particularly in those taking desiccated thyroid hormone. Subclinical hyperthyroidism affects approximately 2% of adults and increases with advancing age, with 3% of adults over 80 years of age being affected. It is characterized by TSH levels lower than the reference range but FT4 and FT3 levels within the normal reference range (19).

In our study, we have some possible limitations, such as limited number of study patients, unequal group distributions, and a single study time point that reduced the internal validity of the study.

CONCLUSION







In our investigation, we have confirmed that the serum concentration of the hormone TSH is lowered while the concentrations of FT3 and FT4 are elevated in patients with latent and pronounced hyperthyroidism compared to the control group of patients of the same age. TSH concentration is decreased in hyperthyroidism and subclinical hyperthyroidism. The serum concentration of FT3 and FT4 is elevated in hyperthyroidism, while in subclinical hyperthyroidism, the serum concentration of FT3 and FT4 is in the reference range.

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PROMJENE KONCENTRACIJA TSH, FT3 I FT4 KOD PACIJENATA SA HIPERTIREOZOM

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SAŽETAK

Uvod: Poremećaji lučenja hormona štitnjače mogu biti hipertireoza (snižene razine TSH i povišene razine FT3 i FT4) i subklinička hipertireoza (snižena koncentracija TSH uz normalan FT3 i FT4).

Cilj: istražiti koncentracije hormona štitnjače (TSH, FT3 i FT4) kod pacijenata sa hipertireozom ili subkliničkom hipertireozom liječenih u Plavoj Klinici u Tuzli.

Materijali i metode: Istraživanjem je obuhvaćeno 120 bolesnika podijeljenih u tri skupine kontrolnu skupinu, skupinu s ispitanicima koji imaju hipertireozu i skupinu bolesnika sa subkliničkom hipertireozom. Analizirana je koncentracija hormona TSH, FT3 i FT4. Određivanje je izvršeno na analizatoru IMMULITE 1 Siemens, a određivanje parametara je urađeno sa imunokemijskom metodom.

Rezultati: Rezultati su pokazali za TSH je postojanje značajnih statističkih razlika između kontrolne skupine i skupine s hipertireozom ($p < 0,0001$) te između kontrolne skupine i skupine sa subkliničkom hipertireozom ($p = 0,0001$), a parametar FT3 pokazao je da postoji statistički značajna razlika između kontrolne skupine i skupine s hipertireozom ($p < 0,0001$), te između bolesnika s hipertireozom i subkliničkom hipertireozom ($p < 0,0001$). Za FT4 smo utvrdili statistički značajnu razliku između kontrolne skupine i skupine s hipertireozom ($p < 0,0001$) te između skupina s hipertireozom i subkliničkom hipertireozom ($p < 0,0001$).

Zaključak: Koncentracija TSH je smanjena kod hipertireoze, kao i kod subkliničke hipertireoze. Serumske koncentracije FT3 i FT4 su povišene u hipertireozu, dok je u subkliničkoj hipertireozu serumska koncentracija FT3 i FT4 u referentnom području.

Ključne riječi: tirotropin, tiroksin, TSH, FT3, FT4, hipertireoza

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