

Frequency and Duration of Hyperthyroidism in Patients in the Endocrinology Counselling Center at Clinical Center Sarajevo

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Background: Hyperthyroidism is a disease of the thyroid gland characterized by elevated levels of thyroid hormones. It is present in 0.5-2% of patients and is ten times more common in women. For patients who have severe symptoms of hyperthyroidism or with a significant risk of complications, antithyroid drugs are recommended, the effect of which affects the duration of the disease. **Objectives:** The goal of this study is to determine the frequency and duration of hyperthyroidism depending on the therapeutic treatment in endocrinological patients. **Methods:** The study is retrospective, clinical, performed in the period 01.01.2019-01.08.2019. at the Endocrinology Counseling Center of the Clinical Center of the University of Sarajevo (KCUS). In a seven-month period of 2002 patients of both sex, 37 patients with hyperthyroidism were analyzed. Data were taken from specialist findings from the Hospital Information System (BIS) of the Endocrinology Counseling Center of the Clinic for Nuclear Medicine and Endocrinology. None of the patients were excluded from the study. In all hyperthyroid patients data on gender, age, duration of hyperthyroidism, type of thyrostatics, presence of elevated thyroid antibody titer, and thyroid ultrasound were analyzed from the medical findings. **Results:** Out of the 2002 endocrinological patients, 37 or 1.85% were diagnosed with hyperthyreosis. Out of 37 patients, 32 (86%) were females and 5 (14%) males, aged 25-89 years. There were 25 patients on thiamazole and 12 on propylthiouracil therapy. The average duration of hyperthyroidism was 22.9 months. There were 23 patients in remission. The average remission lasted 5.9 months (maximum 16, minimum 1 month). Anti thyroglobulin antibodies (anti TgAt) were elevated in 20 patients, thyroid peroxidase antibodies (anti TPOAt) were elevated in 12 patients, while thyrotropin receptor antibodies (anti TSHRAnt) were increased in 20 patients. **Conclusion:** According to our study, hyperthyroidism is frequent and patients in our counseling center stay on medical treatment longer than recommended, because they avoid definitive treatment of hyperthyroidism (radioactive iodine, surgery). Further studies in Bosnia and Herzegovina should monitor the frequency of hyperthyroidism with a larger number of samples, and the frequency of side effects in drug therapy of hyperthyroidism in order to prove the benefits and limitations of definitive treatment.

Keywords: hyperthyroidism, antithyroid therapy, remission.

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1. BACKGROUND

Hyperthyroidism is an increase in circulating thyroid hormones. Thyroid stimulating hormone (TSH) concentrations decrease, and free thyroxine (FT4) and free triiodothyronine (FT3) increase with age (1). Various diseases and conditions lead to hyperthyroidism such as Graves' disease, de Quervain's disease, toxic thyroid adenomas, and other diseases (2, 3). Thyroid hormones have an effect on most tissues and organs, but are thought to have the greatest impact on the cardiovascular system (4). Untreated hyperthyroidism can have symptoms such

as weight loss, tremor, muscle weakness, osteoporosis, and even serious symptoms such as atrial fibrillation and cardiovascular collapse (5). Hyperthyroidism as well as other thyroid diseases in terms of frequency represent a significant public health problem. Hyperthyroidism is present in 0.5–1.3% of endocrinological patients and is ten times more common in women (6). It occurs in pregnancy in a smaller percentage of about 0.4% (6). In the United States (USA), hyperthyroidism occurs in 1.2% of patients, slightly more than one in 100 people (7). In the United States, more than 3 million people have Graves' disease,

and the lowest in the child population is about 41 000, most of them children aged 10-15 (8). According to a meta-analysis conducted in 2014, the prevalence of hyperthyroidism in Europe was 0.75%, while the incidence rate of hyperthyroidism was 51.04 per 100 000 population per year (9). It is more prevalent in the white population than in other races (9). The highest percentage of patients with hyperthyroidism is in the age group of 40 to 60 years, and the female population is most affected (10). In 2016, 1035 patients of all ages were hospitalized in Croatia for hyperthyroidism, according to a report by the Croatian Institute of Public Health (11). Thiamazole or propylthiouracil is most commonly used in therapy, and surgical therapy is the ultimate way to resolve hyperthyroidism. The fact that data on the incidence of hyperthyroidism in Bosnia and Herzegovina has directed the need and goal of our work to determine the incidence and duration of hyperthyroidism in endocrinological patients treated in endocrinological counseling.

2. OBJECTIVE

The goal of this study is to determine the frequency and duration of hyperthyroidism depending on the therapeutic treatment in endocrinological patients.

3. MATERIALS AND METHODS

The study is retrospective, clinical, performed in the period 01.01.2019. to 08.01.2019. at the Endocrinology Counseling Center of the Clinical Center of the University of Sarajevo (KCUS). In the seven-month period of 2002 patients with endocrine diseases, 37 patients with hyperthyroidism, 32 females and 5 males, aged 25 to 89 years, were analyzed. Data were taken from specialist findings from the Hospital Information System (BIS) of the Endocrinology Counseling Center of the Clinic for Nuclear Medicine and Endocrinology KCUS. Inclusion criteria were: patients with established hyperthyroidism who were examined at the Endocrinology Counseling Center. Exclusion criteria were: patients under 18 years of age, patients with subacute thyroiditis. All patients with hyperthyroidism were included in the study. Patients with endocrine disorders other than hyperthyroidism were not included in the study. None of the hyperthyroid patients were excluded from the study. In all hyperthyroid patients, data from medical findings on gender, age, duration of hyperthyroidism, type of thyrostatics, presence of elevated thyroid antibody titer, and ultrasound findings of the thyroid gland were analyzed.

Statistical data processing was done using the computer program Excel 2003 and SPSS 13 for Windows, a computer program for statistical analysis and descriptive statistics. The data were statistically processed so that the following values were determined: mean and standard deviation, minimum and maximum value, Pearson test, t-test and z-test. The results were presented in the form of figures. The significance of the difference for continuous variables was tested by an independent Student t-test. Values of $p < 0.05$ were considered statistically significant.

4. RESULTS

The total number of patients who were first time at the Endocrinology Counseling Center was 2002, from them 37 were diagnosed with hyperthyreosis (1.85%). There were 32 (86%) females among the patients with hyperthyroidism, while there were 5 (14%) males. The mean age of patients was 53.6 years \pm 17.1 years, the oldest patient was 89 years old, while the youngest was 25 years old. There were 25 patients on therapy with thiamazole, while 12 patients were on therapy with propylthiouracil. The average duration of hyperthyroidism was 22.9 months (1.9 years), the longest duration was 102 months while the shortest duration was 3 months. There were 23 patients in remission and 14 without remission, average remission

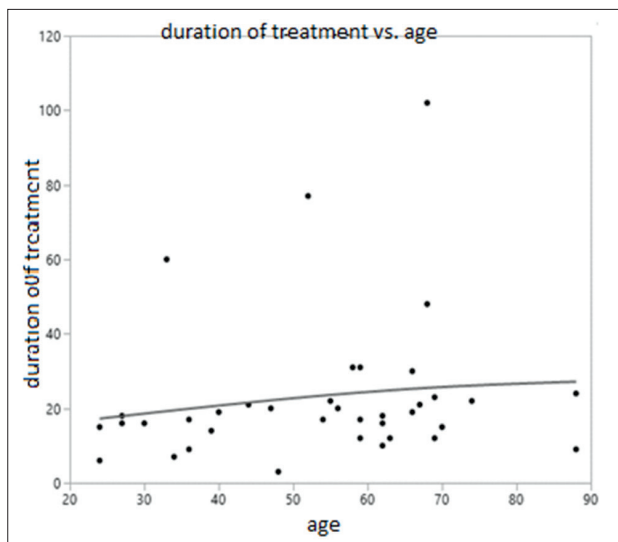


Figure 1. Correlation of therapy duration and age for the whole sample. * Legend: duration of treatment- duration of thyrostatic therapy expressed in months, age- age of patients expressed in years, duration of treatment vs age- duration of thyrostatic therapy expressed in months, in relation to age expressed in years

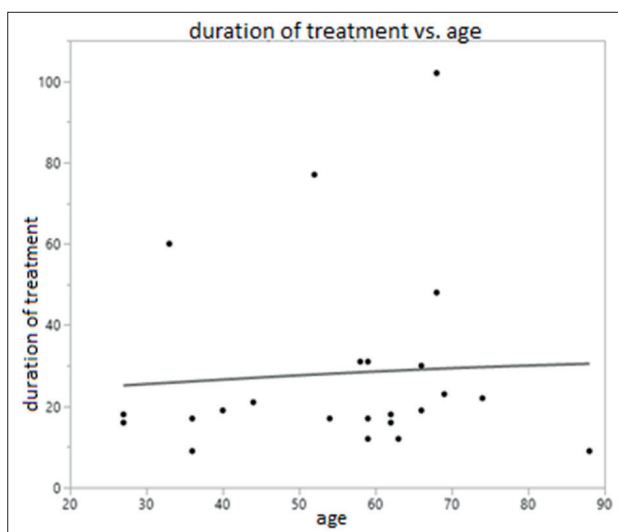


Figure 2. Correlation of therapy duration and age in patients with remission. * Legend: duration of treatment- duration of thyrostatic therapy expressed in months, age- age of patients expressed in years, duration of treatment vs age- duration of thyrostatic therapy expressed in months, in relation to age expressed in years

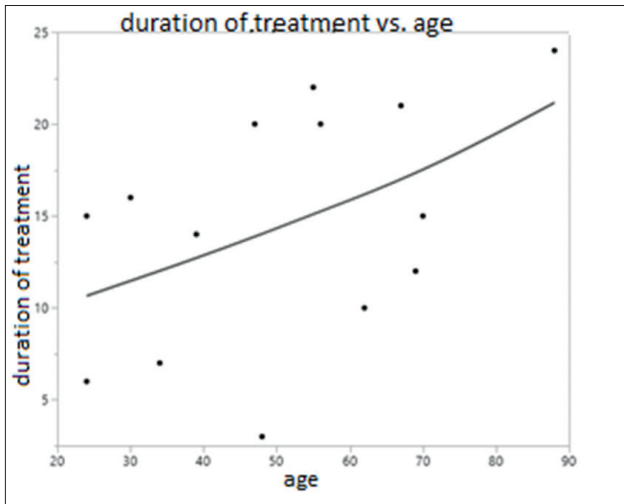


Figure 3. Correlation of duration of therapy and age * Legend: duration of treatment- duration of thyrostatic therapy expressed in months, age- age of patients expressed in years, duration of treatment vs age- duration of thyrostatic therapy expressed in months, in relation to age expressed in years

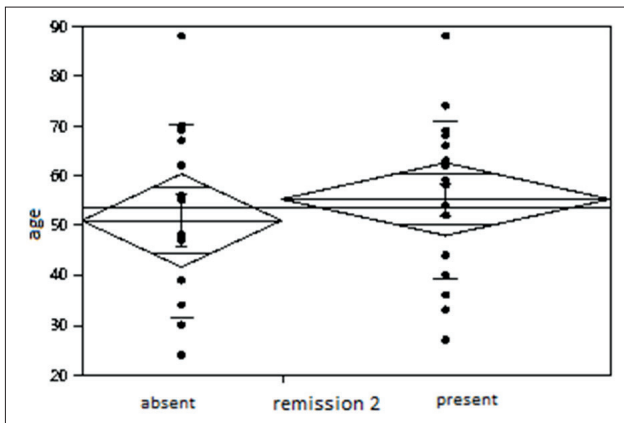


Figure 4. The ratio of the age of patients who had remission and those who had not. * Legend: age- age of patients expressed in years, present- the presence of disease remission, absent- absence of disease remission; remission 2- remission of hyperthyroidism

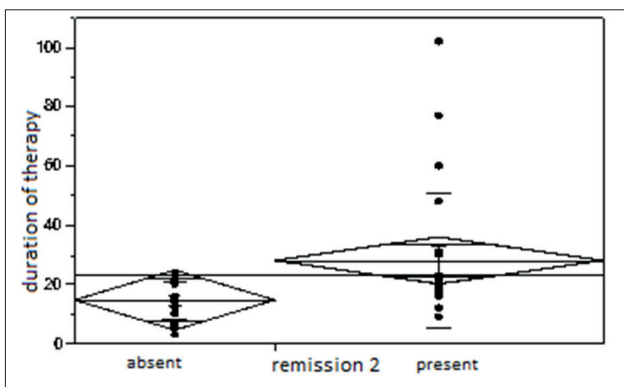


Figure 5. Duration of therapy in relation to the presence of remission. * Legend: duration of therapy expressed in months, present- the presence of disease remission, absent- absence of disease remission; remission 2- remission of hyperthyroidism

duration was 5.1 months \pm 3.4, the longest duration of remission was 16 months, while the shortest duration of remission was 1 month.

Increased antithyroglobulin antibodies (Anti Tg) had

20 patients, and 17 patients had AntiTg in reference range. Thyroid peroxidase antibodies (Anti TPO) were elevated in 12 patients and in 25 patients were in reference range. The value of TRAb was increased in 20 patients and 17 patients had TRAb in the reference.

Thyroid echo findings were within physiological limits in 10 patients, 9 patients had a multinodular goiter, one of whom had retrosternal goiter propagation, 5 patients had a diffuse goiter, 9 patients had a rough parenchymal structure, and 4 patients had the presence of one nodule.

We used the z-test to test the hypothesis whether there is a statistically significant difference in the prevalence of hyperthyroidism in our sample (1.85%) compared to the data found in the literature (1.3%).

1. Correlation of duration of therapy with age

No statistically significant correlation was found between age and duration of thyrostatic therapy. Pearson $r = 0.15$, $p = .38$ (Figure 1.)

2. Correlation of duration of thyrostatic therapy and age in persons with remission

In persons with remission ($n = 23$) there is no statistically significant correlation between the duration of therapy and age, Pearson $r = 0.06$, $p = .77$. The correlation is shown in Figure 2.

3. Correlation of duration of thyrostatic therapy and age in persons without remission

There are 14 patients without remission. The Pearson correlation coefficient is $r = 0.47$, $p = .08$. (correlation is not statistically significant), which is shown in Figure 3.

4. The ratio of the age of patients who had remission and those who did not

The average age of patients who had remission was 55.2 years (SD-15.9 years), and those who did not have remission was 50.9 years (SD-19.3). According to the results of the t test, there is no statistically significant difference in the mean age between the two groups of patients ($t = 0.7$; $p = 0.47$), which is shown in Figure 4.

5. The ratio of the duration of therapy in relation to the occurrence of remission

The average duration of thyrostatic therapy for patients with remission is 28 months (SD-23), and those without remission 14.6 (SD-6.4). According to the results of the t-test, there is a statistically significant difference in the length of therapy of patients with and without remission ($t = 2.1$; $p = .04$). The results are shown in Figure 5.

The ratio of the incidence of remission between men and women shows that men have an 8.6 times higher chance of remission than women (confidence interval 0.4–169). Although the t-test result is not statistically significant ($z = 1.4$, $p = 0.15$).

5. DISCUSSION

We noticed an increase in patients with hyperthyroidism in the Endocrinological Counseling Center. We also observed that drug treatment of hyperthyroidism lasts longer than the optimal recommended duration of about 18 months. The prolonged duration of drug therapy increases the risk of developing allergies to thyrostatics,

as well as the frequency of side effects of thyrostatics. The titration regimen for 12–18 months is the optimal strategy for antithyroid drug therapy (ATD) (12). Our study showed that hyperthyroidism occurs about 7 times more often in women than in men. On the other hand, other studies have shown that hyperthyroidism is even 10 times more common in women than in men (13). However, our study had fewer patients than in other studies.

According to a study by Abraham et al, the average duration of antithyroid drug therapy is 12 to 18 months (14). Our study showed that antithyroid drug therapy in our patients lasted 22.9 months. Furthermore, the longer duration of drug therapy in our patients may be related to the fact that patients refuse or delay definitive treatment due to fear of radiation and the consequences of surgery.

In our study, there were 23 patients in remission and 14 without remission, average remission duration was 5.1 months. Males have an 8.6 times higher chance of remission than females, however due to the small sample, the result is inappropriate to generalize. Additional studies with more male subjects are needed to see if men are really that much more prone to remission than women. Moreover, the study showed that in patients in whom iodine intake is low remission rates may be higher (15). According to previous studies, the incidence of remission with thionamide therapy is below 40% in people taking therapy for up to two years, however, according to recent studies, remission has been shown to be as high as 84% in people taking thionamide from 5 to 10 years (16, 17).

Patients also underwent TRAb, which confirms the diagnosis of Graves' disease (18), and our study showed that increased TRAb occurs in 20 patients, which proves that Graves is the most common cause of hyperthyroidism.

Treatment of hyperthyroidism begins with antithyroid drugs, thiamazole or propylthiouracil, and beta-blockers in order to achieve a euthyroid state. Thiamazole is now used almost exclusively due to its longer action since it can be used once daily, faster efficacy, and small incidence for the occurrence of adverse reactions. Thiamazole is not recommended to use in the first trimester of pregnancy (19), and patients who have fewer side effects to thiamazole should use alternative antithyroid drugs (20). The initial cycle of treatment with antithyroid drugs in adults usually lasts from 12 to 18 months, and in children up to 36 months, because it is more difficult to achieve remission in children (21,22,23). When patients on thiamazole therapy, with very severe hyperthyroidism caused by Graves' disease, reach a euthyroid state, definitive therapy—radioactive iodine therapy or surgery is suggested as the next step in the treatment. A one- or two-year therapy cycle with thiamazole or long-term thiamazole therapy are reasonable alternatives but are not applicable to all patients (24).

If definitive therapy is to be applied, radioactive iodine is suggested in the absence of moderate or severe ophthalmopathy, due to lower costs and complications as opposed to surgical treatment. For patients who tolerate symptoms of hyperthyroidism and who are not at risk for complications of hyperthyroidism, radioactive iodine can be

administered as initial therapy – without premedication with antithyroid drugs. Initial antithyroid therapy is an alternative option and a better choice for patients with mild disease and small goiters who are very likely to achieve remission after one year of therapy (25).

For hyperthyroid patients with very large or obstructive goiters, surgery is suggested. It is also indicated for patients who have allergic reactions to antithyroid drugs and who are unable or unwilling to administer radioactive iodine. Surgery is also recommended for people who have active ophthalmopathy (26).

Patients who wish to become pregnant in the near future are advised to consider radioactive iodine therapy or surgery, six months before planning a pregnancy, to avoid the need to take antithyroid drugs during pregnancy. If radioactive iodine and surgery are not the preferred option, propylthiouracil is the antithyroid drug of choice for use during the first trimester of pregnancy and may be continued during pregnancy (27).

Regardless of which therapeutic treatment is applied, the initial monitoring that accompanies therapeutic treatment consists of periodic clinical testing and measurement of FT4 and FT3 levels (28). Measurement of TSH levels may show an erroneous picture in initial monitoring, as it may remain low for weeks or months, even when patients are euthyroid or even hypothyroid according to biochemical measurements, with normal or low FT4 levels.

A very common consequence of the definitive treatment of Graves' disease is permanent hypothyroidism that requires lifelong therapy with thyroid hormones. Therefore, patients often choose between long-term antithyroid therapy and lifelong levothyroxine therapy (29). Long-term antithyroid drug therapy is an increasingly researched topic in the world. Most studies support the use of long-term antithyroid drug therapy, but in small doses, in patients with a milder clinical picture, who do not have allergic reactions and without the risk of complications. Long-term therapy with antithyroid drugs in higher doses over time leads to the appearance of side effects, so in this case, definitive treatment is inevitable.

Our study has several limitations. It was performed in a short period of time, with a small number of patients. Furthermore, some patients after 01.08.2019. did not undergo definitive treatment but continued with therapy. On the other hand, our study has benefits such as the fact that there are not enough studies in Bosnia and Herzegovina on the incidence of hyperthyroidism, and we consider this paper as an initial step in the study of hyperthyroidism in the population of Bosnia and Herzegovina.

This research should be continued in order to create a national registry of hyperthyroid patients and to form a treatment strategy for these patients based on current guidelines. This would allow a systematic approach to the definitive solution of this public health problem.

6. CONCLUSION

According to our study, hyperthyroidism is frequent and patients in our counseling center stay on medical

treatment longer than recommended, because they avoid definitive treatment of hyperthyroidism (radioactive iodine, surgery). Further studies in Bosnia and Herzegovina should monitor the frequency of hyperthyroidism with a larger number of samples, and the frequency of side effects in drug therapy of hyperthyroidism in order to prove the benefits and limitations of definitive treatment.

- **Patient Consent Form:** *The authors certify that they have obtained all appropriate patient consent forms.*
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