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TREATMENT OF SUBCLINICAL HYPERTHYROIDISM SIGNIFICANTLY REDUCES THE RATE AND SYMPTOMS OF ASSOCIATED CARDIOVASCULAR ABNORMALITIES

Said GAZIBEGOVIĆ[1]
Amra JAKUBOVIĆ-ČIČKUŠIĆ[2]
Zumreta KUŠLJUGIĆ[3]
Fahir BARAKOVIĆ[3]

[1] *Health Center Odžak, Odžak*

[2] *Department of Nuclear Medicine, University Clinical Center Tuzla, Tuzla*

[3] *Department of Cardiology, University Clinical Center of Tuzla, Tuzla*

Bosnia and Herzegovina

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Correspondence to:
Said GAZIBEGOVIĆ, MD, MSc
Health Center Odžak
76290 Odžak
Bosnia and Herzegovina

phone: +387 63 438 776
email: said2008@net.hr

ABSTRACT

Background: The treatment of subclinical hyperthyroidism (SH) is still controversial since there are no huge clinical trials that tried to assess the effects of therapy of SH.
Aim: We aimed to determine whether a frequency and symptoms of cardiovascular abnormalities commonly associated with hyperthyroidism will reduce after the treatment with methimazole in a cohort of patients with established and untreated SH.
Methods: We prospectively evaluated 29 patients with recently diagnosed SH that were naïve to any treatment directed against over production of thyroid hormones. We evaluated each patient by assesing the rate of specific symptoms, clinical examination, electrocardiography, heart ultrasonography and determination of thyroid hormones and antibodies.
Results: The mean in our sample was 49±13 years with 21 (79.32%) women. The average duration of methimazole treatment was 7±1 months. Mean values of all thyroid hormones and thyroid antibodies significantly declined after the treatment ($p<0.05$). A significant decrease in frequency of palpitation, irregular heart beat and dyspnoea was observed in patients after the treatment ($p<0.001$). There was no difference in mean values of diastolic pressure before and after the treatment, however systolic pressure and heart rate declined significantly after the treatment ($p<0.0001$). A clear reduction in LV mass, interventricular septum thickness and thickness of posterior wall of LV was demonstrated as a response to treatment of subclinical hyperthyroidism ($p<0.001$). Supraventricular premature beats and sinus tachycardia completely disappeared after the treatment ($p<0.002$). Although there was a clear tendency for a reduction in frequencies of paroxysmal supraventricular tachycardia, atrial fibrilation and right bundle branch block, it was not statistically significant.
Conclusion: Cardiovascular abnormalities associated with SH are significantly reduced after treatment with methimazole and achieving euthyroidism. Our results indicate that treatment of this syndrome is justified as it may reverse potentially harmful effects on cardiovascular system.

Key words: *subclinical hyperthyroidism; treatment; cardiovascular; echosonography; methimazole*

INTRODUCTION

Subclinical hyperthyroidism (SH) is a biochemical syndrome characterized by a low or suppressed level of thyroid stimulating hormone (TSH) along with a presence of normal levels of free circulating hormones of thyroid gland. It is divided into two etiological forms: endogenous, which is a consequence of various diseases of thyroid gland and exogenous, which is a consequence of suppressive or substitution therapy with L-thyroxin.[1]

SH is a relatively common condition especially in mid and old age.[2] It is recognized as a separate clinical entity after second and third generations of TSH assays came into routine use since it was only then possible to distinct between low and normal concentration of TSH. Higher sensitivity of TSH assays as well as more frequent evaluation of serum TSH resulted with increasing incidence of this particular syndrome.

Table 1. *Baseline characteristics of patients*

Parameter		Mean ± SD
Age	*years*	48.96±12.57
Sex (ratio)	*M/F*	6/23
FT3	*pmol/L*	6.63±0.79
FT4	*pmol/L*	17.84±3.0
TSH	*mU/L*	0.09±0.10

TSH – thyrostimulating hormone

Etiology, pathophysiology, prevalence, risk factors and consequences of SH remain elusive.[3]

SH often manifest with signs and symptoms associated with oversecretion of thyroid hormones.[4] Most of the patients with SH have symptoms typical for true hyperthyroidism which include: dyspnea, intolerance of heat, irritability, palpitations, tremor, weight loss, food craving and increased bowel movements. Palpitation is one of the symptoms most frequently described with SH.[5] Nevertheless, the clinical presentation of this syndrome is not always clear and it is not unusual that patient has either few or no symptoms.[6]

The treatment of this syndrome is still controversial. There are no huge clinical trials that tried to assess effects of therapy of SH. Most papers try to explain the need for treatment in a somewhat indirect way.[4,6,7]

We aimed to determine a frequency of cardiovascular abnormalities commonly associated with hyperthyroidism in a cohort of patients with established and untreated SH prior and after the treatment with methimazole. We hypothesized that treatment of SH significantly reduces the frequency and symptoms of associated cardiovascular abnormalities.

METHODS

We prospectively evaluated 29 patients with recently diagnosed SH that were naïve to any treatment directed against over production of thyroid hormones. SH was diagnosed if patients had 2 consecutive measurements of TSH lower than normal (<0.32 mU/L) and 2 consecutive measurements of thyroid hormones within the normal range. Measurements were separated by time period of at least 3 months. We recruited patients of both genders that were referred for evaluation in Department for Nuclear Medicine in University Clinical Center of Tuzla. We excluded all patients that were previously diagnosed with either thyroid or cardiovascular disease.

Each patient was assessed for presence of the subjective symptoms (palpitation, chest pain, irregular heart beat and dyspnea) in the period of 3 months prior to evaluation on initial visit or in the period since beginning the treatment on the follow up. We clinically evaluated each patient which included determination of resting heart rate and blood pressure.

Each patient was also assessed by using standard 12-channel electrocardiogram which was later reviewed by an experienced cardiologist for presence of rhythm and conduction abnormalities, changes in ST segment and ventricular hypertrophy. History of a confirmed rhythm abnormalities such as supraventricular tachycardia, atrial fibrillation or supraventricular premature beats within the last 3 months was also noted.

Experienced cardiologist also performed a standard heart echosonography and we monitored values of ejection fraction (EF), diastolic left ventricle diameter (LVDd), diastolic intraventricular septum thickness (IVSd), diastolic posterior wall thickness (PWd) and shortening fraction (FS).

Blood sample was also drawn from each patient and serum concentrations of TSH, free T3, free T4, thyroid peroxydase antibodies (TPOAt) and thyroglobulin antibodies (TgAt) were determined using sensitive assays. TSH (ref.range: 0.32-5.2 mU/L) was determined by using radioimmuno assay (RIA) with a lower limit of detection of 0.03 mU/L (Ultrasensitive TSH II, Assay System, Abbott Laboratories, Inc, Abbott Park, IL). Free T3 (ref.range: 2.8-6.1 pmol/l) and free T4 (ref.range: 10.3-24.5 pmol/l) were determined by fluoroimmuno

Table 2. *Comparison of levels of thyroid hormones and thyroid antibodies prior and after the treatment with methimazole*

Parameter	Before treatment	After treatment	p-value
FT3	6.63±0.79	4.65±0.54	0.0001
FT4	17.87±3.00	13.88±1.79	0.0001
TSH	0.09±0.10	1.25±0.60	0.0001
TgAt	43.88±27.66	34.33±20.30	0.03
TPOAt	422.66±277.30	84.55±42.49	0.002

Paired t- test

Table 3. *The frequency of cardiovascular symptoms in patients before and after the treatment*

Symptom	Before treatment	After treatment	p-value
Palpitation	18	3	<0.0001
Chest pain	6	1	0.06
Irregular heartbeat	17	0	<0.0001
Dyspnea	15	4	0.001

McNemar test

assay based on Delphia technique (Farmacia, Wallac Oy, Turku, Finland). TPOAt (ref.range: up to 50 IU/L) was determined by using a direct RIA method (RSR Limited, Cardiff, UK) while TgAt (ref.range: up to 70 IU/L) was determined by using radioreceptor assay (RSR Limited, Cardiff, UK).

We assessed patients with the above mentioned battery of tests prior to the treatment and after treating them with a 10 mg of methimazole for as long as needed to achieve euthyroidism defined by normalization of TSH levels.

All statistical analysis procedures were performed using Medcalc 9.2 (MedCalc Software, Mariakerke, Belgium). Standard test of descriptive statistics were used for determination of baseline characteristics of groups. Since we were comparing paired samples, between-group differences in frequencies were investigated by using McNemar's test. Paired t-test was used for comparison between numerical variables. Statistical level of 95% ($p<0.05$) was considered as significant for all performed tests.

RESULTS

The mean age in our sample of patients with SH was 49±13 years. The youngest patient was 19 and oldest was 67 years old. There were 21 (79.32%) women and 6 (20.68%) men within our sample. Baseline characteristics of patients are displayed in Table 1.

The most frequent thyroid disease behind SH was autonomous functional node (AFN) which was found in 12 patients (41.4%), while Graves-Basedow disease and multinodular toxic goiter (MNG) were found in 7 patients, each (24.1%). We have not found any overt thyroid disease in the remaining 3 patients (10.3%).

The average duration of methimazole treatment was 7±1 months with the shortest time to achieving euthyroidism of 5 and the longest time of 9 months.

The comparison of levels of thyroid hormones and thyroid antibodies prior and after the therapy is demonstrated in table 2. As observable, mean values of all thyroid hormones and thyroid antibodies significantly declined after the treatment.

We compared frequencies of subjective cardiovascular symptoms before and after the treatment as demonstrated in table 3. We observed a significant decrease in frequency of palpitation, irregular heartbeat and dyspnoea in patients after the treatment when compared with frequency prior to therapy.

A comparison of heart rate and blood pressure mean values before and after the treatment is displayed in table 4. As observable we have not found any difference in mean values of diastolic pressure before and after the treatment, however systolic pressure and heart rate declined significantly after the treatment.

Measurements obtained during heart echosonography prior and after the treatment were also compared as demonstrated in table 5. There was a significant improvement in all monitored parameters after the treatment when compared to measurement prior to the therapy.

We compared the frequency of rhythm and conduction abnormalities in patients before and after the

Table 4. *Comparison of mean values of blood pressure and heart rate in patients before and after the treatment*

Parameter	Before treatment	After treatment	p-value
Systolic BP	137.48±12.26	128.89±8.18	<0.0001
Diastolic BP	73.55±9.04	73.44±5.42	0.93
Heart rate	86.44±9.22	75.79±4.21	<0.0001

Paired samples t-test; BP-blood pressure

Table 5. *Comparison of heart echosonography parameters in patients before and after the treatment*

Echosonography parameter	Before treatment	After treatment	p-value
EF	57.79±7.40	55.72±6.16	NS
LVDd	5.02±0.54	4.17±0.50	<0.0001
IVSd	1.019±0.66	0.940±0.53	<0.0001
PWd	1.073±0.80	0.974±0.55	<0.0001
FS	38.13±5.93	35.37±4.25	0.0002

EF-ejection fraction; LVDd-diastolic left ventricle diameter; IVSd-diastolic interventricular septum thickness; PWd – diastolic posterior wall thickness; FS-shortening fraction; NS-not significant

treatment (table 6). We have found that supraventricular premature beats and sinus tachycardia completely disappeared after the treatment. Although there was a clear tendency for a reduction in frequencies of PTSV, AF and RBBB, it was not statistically significant.

DISCUSSION

SH may cause a wide spectrum of cardiovascular abnormalities.[5] Short term effects of thyroid hormones are of electrophysiological nature and may lead to occurrence of sinus tachycardia, premature heart beats of atrial origin and atrial fibrillation. Long term effects may result in increased left ventricular mass and increased heart strain leading to systolic and diastolic dysfunction, especially during the physical exertion.[5]

Several papers reported that continuous 24-hours ECG almost characteristically shows increased heart rate as well as exaggerated response to physical exertion, although the heart rhythm is usually preserved. The analysis of heart rate variability revealed an imbalance between sympathetic system and vagus with the dominance of the former one.[1,8,9]

Changes in blood pressure are also common in patients with SH. They are characterized by the raise of systolic and decrease of diastolic blood pressure.[10] These hemodynamic changes are the consequence of a significant increase of stroke volume and pronounced reduction in peripheral vascular resistance.

Various abnormalities of heart rhythm are also described as a consequence of subclinical hyperthyroidism; still the atrial fibrillation is the most frequent one.[11,12] Refractory period of atrial heart cells is found to be reduced which may explain this tendency.[9]

It is not completely clear why there is increase in the mass of the left ventricle (LV). It is a general assumption that development of LV hypertrophy is response to chronic hemodynamic strain due to a mild hyperkinetic state of the cardiovascular system.[13,14] Abnormalities in morphology and function of LV are promptly normalized after achieving euthyroidism and are significantly reduced after treatment with β blockers.[4,15] SH is also characterized by an increased LV ejection fraction (EF) in resting state, but paradoxically, EF significantly drops during physical exertion. After achieving euthyroid state, EF during physical exertion returns to normal values.[16] We also demonstrated a clear reduction in LV mass, interventricular septum thickness and thickness of posterior wall of LV as a response to treatment of SH (Table 5). EF values did not differ significantly but we were measuring it in resting state.

The present study is an attempt to assess the impact of treatment of SH on the reduction of known cardiovascular abnormalities that are commonly seen in these patients. Our data may provide additional evidence that treatment of this syndrome is indeed justified. We have used moderate dose of methimazole (10 mg daily) and we achieved excellent response in all of our patients that resulted in a decrease of levels of thyroid hormones and antibodies and a significant increase in TSH levels (table 2). However, it is important to emphasize that average response time to administered treatment appears longer than usual. The patients were indeed scheduled for regular follow up after 2 months. However, most of them reported back after 6 months or more, due to the complicated scheduling system in our health care system. This is why the response time appears prolonged.

Patients with low or suppressed levels of TSH do suffer from a mild form of tissue hyperthyroidism and they do have many cardiovascular symptoms. This was confirmed in several studies that investigated the consequences of SH on cardiovascular system.[10,17-19] Our results also confirm this fact since most of our patients have had at least one cardiovascular symptom (table 3) and this was a leading reason they were seeking medical help. Palpitation dominated as a symptom in our patients which is a finding that is similar to those reported by other investigators.[17-19]

Table 6. *Frequency of rhythm and conduction abnormalities in patients before and after the treatment*

Abnormality	Before treatment	After treatment	p-value
SVES	10	0	0.002
Sinus tachycardia	15	0	<0.0001
PTSV	3	1	0.50
AF	3	2	0.25
RBBB	3	0	0.89

SVES-supraventricular extrasystole; PTSV-paroxysmal supraventricular tachycardia; AF-atrial fibrilation; RBBB-right bundle branch block

Biondi et al reported significant changes in ST segment and T-wave in the absence of angina.[1] Myocardial ischemia is probably caused by increased metabolic need of the thyrotoxic myocard.[15] Nevertheless, our patients did not have any changes in ST segment or T wave abnormalities, but 6 of them did have a subjective sensation of chest pain (table 3) prior to the therapy. After the treatment, this sensation persisted in only one patient. Still, in the absence of objective signs of ischemia it is hard to reliably interpret the significance of this finding.

Our results also revealed that normalization of TSH reduces the occurrence of abnormalities of heart rhythm and rate. Frequency of sinus tachycardia and atrial premature beats reduced significantly after treatment, and other abnormalities also demonstrated a trend towards a reduction in rate of occurence (Table 6). Another study reported 10 patients that were treated for SH for a time period of 6 months. After the treatment a reduction in heart rate and occurrence of premature heart beats was reported.[20]

Faber et al reported that after treating SH they found a significant reduction in heart rate and an increase in systolic vascular resistance.[21] Systolic blood pressure and heart rate also decreased in our patients after treatment (Table 4).

It is important to emphasize several limitations of this paper. Sample size is the obvious limitation; however the study protocol included several tests of cardiovascular status which were not easy to carry out in our particular settings. Also, the rather complicated referral system prevented us from following up patients and their response to therapy in optimal time intervals. Nevertheless, we do not think that these drawbacks have a significant impact on the main conclusions of this study.

Cardiovascular abnormalities associated with SH are significantly reduced after treatment with methimazole. Frequencies of subjective symptoms, values of heart rate and systolic blood pressure are also reduced as a response to treatment. Echosonographic features of the heart in patients with SH also improve after therapy. Our results indicate that treatment of this syndrome is justified as it may reverse potentially harmful effects on cardiovascular system.

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