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Decreased ultrasound echogenicity as a thyroid hypofunction marker and correlation with autoantibody levels

Smanjena ultrazvučna ehogenost kao pokazatelj hipofunkcije štitaste žlezde i korelacija sa nivoima autoantitela

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Abstract

Background/Aim. The value of ultrasound in functional disorders can be significant. That is why the question arises on the use of ultrasound examination of thyroid gland and its echogenicity as a screening method in early detection of disfunctions, of the gland primarily subclinical and clinical forms of hypothyreoidism. The objective of this paper was to determine antibodies of thyroid peroxidase (anti-TPO) and thyroglobuline antibodies (anti-TG) increase frequency in relation to the character of ultrasound echogenicity as well as to estimate the frequency of subclinically and clinically obvious hypothyreoidism in relation to the changed echogenicity. **Methods.** Study included 656 patients in outpatient clinic during 2014. All examinees underwent ultrasound examination of thyroid gland, the blood was taken for determination of free thyroxine (FT4), thyroid-stimulating hormone (TSH), anti-TPO and anti-TG. The patients were divided into two groups; the group A with normal echogenicity of thyroid gland tissue, and the group B with decreased echogenicity. The group B was divided into two subgroups, B1 with a mildly decreased and B2 with significantly decreased echogenicity. **Results.** TPO antibody, TSH and TG antibody positivity and their mean values in the group B were significantly higher, as well as in subgroups B1 and B2, in relation to the group A ($p < 0.001$). In the group A, only 4 (1%) examinees were indicated with subclinical hypothyreoidism. In the group B, the sublinical hypothyreoidism was indicated in 42, while the clinical hypothyreoidism was indicated in 16 examinees. Fifty-eight (25%) examinees suffered from thyroid gland altered function. In the subgroup B1, 16 examinees were indicated with subclinical and 4 with clinical hypothyreoidism. Twenty (11%) examinees suffered from altered thyroid function. In the group B2, the subclinical hypothyreoidism was found in 26 examinees, while the clinical hypothyreoidism was found in 12. Thirty-eight (76%) examinees suffered from altered thyroid function. **Conclusion.** The ultrasound screening of thyroid gland plays an important role in early detection of thyroid disfunction, i.e., sublinical and clinical hypothyreoidism. Decreased ultrasound echogenicity represents the significant marker of altered thyroid gland function. In these persons we have determined the high percentage of subclinical and clinical hypothyreoidism frequency.

Key words:
thyroid gland; hypothyroidism; ultrasonography; thyroid hormones; sensitivity and specificity.

Apstrakt

Uvod/Cilj. Vrednost ultrazvučnog pregleda kod poremećaja funkcije štitaste žlezde može biti velika. Zato se postavlja pitanje korišćenja ultrazvučnog pregleda kao skrining metode u ranom otkrivanju poremećaja funkcije žlezde, pre svega supkliničke i manifestne hipotireoze. Cilj ove studije bio je da utvrdi povećanje tiroid peroksidaza antitela (anti-TPO) i tireoglobulinskih antitela (anti-TG) u odnosu na ultrazvučne ehogenosti, kao i učestalost subkliničke i kliničke hipotireoze u odnosu na izmenjenu ehogenost. **Metode.** U ispitivanje je bilo uključeno 656 bolesnika tokom 2014. Kod svih ispitanika urađen je ultrazvučni pregled štitaste žlezde i određene vrednosti slobodnog tiroksina (TT4), tiroid-stimulišućeg hormona (TSH), anti-TPO i anti-TG. Ispitanici su bili podeljeni u dve grupe. Grupu A čine su osobe sa normalnom ehogenošću tkiva štitaste žlezde, a grupu B osobe sa smanjenom ehogenošću. Grupa B podeljena je bila u dve podgrupe: B1 sa umereno smanjenom ehogenošću i B2 sa značajno smanjenom ehogenošću. **Rezultati.** Srednje vrednosti TSH, anti-TPO i anti-TG bile su značajno više u grupi B, I podgrupama B1 i B2, u odnosu na grupu A ($p < 0.001$). Samo 4 (1%) ispitanika u grupi A su označena kao subklinička hipotireoza. U grupi B subklinička hipotireoza je dijagnostikovana kod 42 ispitanika, a hipotireoza kod 16 ispitanika, što znači da je 58 (25%) ispitanika imalo izmenjenu funkciju štitaste žlezde. U podgrupi B1 subklinička hipotireoza je nađena kod 16, a hipotireoza kod 4 ispitanika,

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odnosno njih 20 (11%) je imala izmenjenu funkciju žlezde. U podgrupi B2, supklinička hipotireoza nađena je kod 26, a hipotireoza kod 12 ispitanika, njih 38 (76%) imalo je izmenjenu funkciju štitaste žlezde. **Zaključak.** Ultrazvučni skrining štitaste žlezde ima važnu ulogu u ranoj detekciji izmenjene tireoidne funkcije, pre svega supkliničke i manifestne hipotireoze. Smanjena ultrazvučna ehogenost tireoidnog tkiva značajan je marker izmenjene funkcije. Kod ovih osoba našli smo značajno veću učestalost supkliničke i kliničke hipotireoze.

Ključne reči:
tireoidna žlezda; hipotireoidizam; ultrazvuk; tireoidna žlezda, hormoni; osetljivost i specifičnost.

Introduction

Ultrasonography represents very frequently used examination method in diagnostic procedure of various thyroid gland diseases. This method has practically no restrictions and it is available and relatively cheap. That is why it is applied in patients without pronounced symptoms of the disease, but also in those with uncharacteristic symptoms and signs like fatigue, dizziness, vertigo, irritation, anxiety, aggravated swallowing and breathing, irregular menstrual periods, heart rhythm alterations, blood pressure rise and plasma lipids level rise. These are sometimes the signs of some thyroid gland diseases.

Ultrasound method is a sovereign method in diagnostics of morphological thyroid gland changes. Its value in functional disorders diagnostics and diagnostics of inflammatory processes can also be significant. That is why the question arises on the use of ultrasound examination of thyroid gland and on the estimation of its echogenicity as a screening method in early detection of disfunctions, primarily subclinical and clinical forms of hypothyreoidism. Results of decreased thyroid gland tissue echogenicity and thyroid-stimulating hormone (TSH) level increase could be the early signs of thyroid gland function failure and the subclinical hypothyreoidism diagnosis, and are significant when having in mind its tendency to progress into the clinically manifested hypothyreoidism. Moreover, this examination method can be of significant assistance in discovering autoimmune thyroiditis (AT) where the fine-needle biopsy (FNB) diagnosis is recognized as a golden standard.

Decreased echogenicity of the thyroid gland tissue is considered specific ultrasound result in autoimmune thyroiditis, but also in hypofunction of the thyroid gland [1–4]. Accuracy and reliability of this kind of estimation are still not clear enough. The increase of antibodies level, first of all thyroid peroxidase (anti-TPO), represents the important parameter in diagnostics of these kinds of disorders [5]. Other irregularities in the ultrasound scans, like nodules with or without decrease of tissue echogenicity, can also be the signs of altered thyroid gland function [6].

The objective of this paper was to determine anti-TPO and thyroglobuline antibodies (anti-TG) increase frequency in relation to the character of ultrasound echogenicity as well as to estimate the frequency of subclinically and clinically obvious hypothyreoidism in relation to the changed echogenicity.

Methods

Study included 656 (622 female and 34 male) outpatients aged 17–68 years, examined at the specialized outpatient facility and at the Ultrasound Diagnostics Cabinet of the Polyclinic Department of the Clinic of Endocrinology, Clinical Center Niš, during 2014. The testing excluded persons already suffering from thyroid gland disfunction as well as persons with indicated increase of thyroid gland function in the course of our testing. All examinees underwent ultrasound examination of thyroid gland, the blood was taken for the lab analysis and for determination of free thyroxine values (FT4), TSH, to anti-TPO and anti-TG.

Ultrasound examination of thyroid gland was always performed by the same ultrasonographist, in neck hyperextension, on ALOKA SSC-390 ultrasound device with a 7.5MHz ultrasound probe for surface tissues. Lab analyses were performed in the Institute of Nuclear Medicine – Clinical Center Niš (FT4 and TSH by Delfia, 1230 Arcus fluorometer, and anti-TPO and anti-TG by RIA, Clinigamma 1272).

On the basis of the ultrasound results and estimated echogenicity done by a sonographist, the patients were divided into two groups. The group A comprised examinees with estimated normal echogenicity of thyroid gland tissue, while the group B comprised examinees with decreased echogenicity of thyroid gland tissue. The group B was divided into two subgroups, B1 with a mildly decreased echogenicity – lower than the one in the connective tissue, but higher than the neck muscles echogenicity (*m. sternocleidomastoideus*) and B2 – significantly decreased thyroid gland tissue echogenicity – the same or lower echogenicity than the one in neck muscles.

Results was expressed as mean ± standard errors of mean (SEM). Significance of differences between the groups was determined by Student's *t*-test and Mann-Witney *U* test for continuous data. Statistically significant differences were assumed at p less than or equal to 0.05. Degrees of association between continuous variables were evaluated by Spearman's Rank Correlation analysis.

Results

On the basis of the thyroid gland ultrasound screening and estimated echogenicity, the group A comprised 424 (64.6%) patients with normal ultrasound echogenicity. The group B, with the estimated decreased ultrasound echogenicity, comprised 232 (35.4%) patients. The subgroup B 1 comprised 182 (27.7%) patients, and the subgroup B2, with significant hypoecogoenic ultrasound results comprised 50 (7.7%) patients.

In the group A, the increase of anti-TPO value was indicated in 36 (8.5%) examinees while the positive anti-TG were indicated in 44 (10.4%) examinees. In the group B,

with decreased thyroid gland echogenicity, the increase of anti-TPO was indicated in 112 (48.3%), and the positive results of anti-TG in 96 (41.4%) examinees. In the group B1 with decreased thyroid gland echogenicity the increased value of anti-TPO was indicated in 68 (37.3%) examinees, and the positivity of the anti-TG in 56 (30.7%) examinees. In the group B2 with the significantly decreased thyroid gland echogenicity the increase of anti-TPO value was found in 44 (88.0%), and positivity of anti-TG in 40 (80.0%) examinees. There is a significantly higher percentage of examinees with the increase in anti-TPO and anti-TG positivity in the group B, as well as in the subgroups B1 and B2 in relation to the group A ($p < 0.01$ and $p < 0.001$, respectively). There was also statistically significant higher percentage of examinees with the increase in anti-TPO antibodies and anti-TG positivity in the subgroup B2 in relation to the subgroup B1 ($p < 0.001$). The results are shown in Table 1.

There were also the significant differences in mean values of tested parameters: of anti-TPO, FT4 and TSH.

In the group A, the mean value of anti-TPO was 58.5 ± 18.4 U and in the Group B 339.3 ± 57.8 U. The mean value of anti-TPO in the group B1 was 248 ± 45.9 U, and in the group B2 670 ± 116.7 U. Statistically significant higher values of anti-TPO were observed in the groups B, B1 i B2 in relation to the group A as well as statistically significant higher values of the TPO in the group B2 in relation to the group B1 ($p < 0.001$). The mean value of FT4 in the group A was 14.6 ± 5.5 nmol/L and in the group B 10.1 ± 2.9 nmol/L. The mean value of FT4 in the group B1 was 11.2 ± 3.4 nmol/L and in the group B2 8.8 ± 3.8 nmol/L. The statistically significant lower values of FT4 were observed in the groups B, B1 i B2 in relation to the group A as well as the statistically significant lower values of FT4 in the group B2 in relation to the group B1 ($p < 0.001$). The mean value of TSH in the group A was 1.05 ± 0.34 mIU/L, in the group B 5.04 ± 1.98 mIU/L, in the group B1 3.82 ± 2.12 mIU/L and in the group B2 8.75 ± 4.36 mIU/L. The statistically significant higher values of TSH were observed in the groups B, B1 and B2 in relation to the group A, as well as statistically significant higher values of TSH in the group B2 in relation to the group B1, ($p < 0.001$). The results are shown in Table 2.

In relation to TSH values in the group with normal echogenicity, there were 420 (99%) patients with value below 4 mIU/L. There were only 4 patients with values of 4–10 mIU/L, while there was no one with the values over 10 mIU/L. In the group with decreased echogenicity there were 174 (75%) examinees with TSH values below 4 mIU/L, 42 (18.1%) with 4–10 mIU/L and 16 (6.9%) were with TSH values higher than 10 mIU/L. In the group with mildly decreased echogenicity, 162 (75%) patients were with TSH values lower than 4 mIU/L, 16 (8.8%) patients were with TSH values of 4–10 mIU/L, and 4 (2.2%) patients with values higher than 10 mIU/L. In the group with significantly decreased echogenicity 12 (24%) examinees were with TSH values lower than 4 mIU/L, 26 (52%) examinees with 4–10 mIU/L and 12 (24%) were with the values higher than 10 mIU/L. The results are shown in Table 3. Consequently, in the group with normal echogenicity only 4 (1%) examinees were indicated with subclinical hypothyreoidism. In the group with decreased echogenicity the sublinical hypothyreoidism was indicated in 42 examinees while the clinical hypothyreoidism was indicated in 16 examinees. Fifty eight (25%) examinees suffered from thyroid gland altered function. In the group with mildly decreased echogenicity, 16 examinees were indicated with subclinical and 4 with clinical hypothyreoidism.

Table 1

Number of patients in relation to ultrasound echogenicity and anti-TPO and anti-TG presence

Ultrasound echogenicity	Number of patients n (%)	Anti-TPO increased n (%)	Anti-TG positive n (%)
Normal echogenicity (group A)	424 (64.6)	36 (8.5)	44 (10.4)
Decreased echogenicity (group B)	232 (35.4)	112 (48.3**)	96 (41.4**)
Mildly decreased echogenicity (subgroup B1)	182 (27.7)	68 (37.3)*	56 (30.7)*
Significantly decreased echogenicity (subgroup B2)	50 (7.7)	44 (88.0)**†	40 (80.0)** †

***statistically significant difference in relation to the group A ($p < 0.01$); **statistically significant difference in relation to the group A ($p < 0.001$); †statistically significant difference in relation to the group B1 ($p < 0.001$).**
Anti-TPO – thyroid peroxidase antibodies; anti-TG-thyroglobuline antibodies.

Table 2

Mean values of thyroid peroxidase antibodies (anti-TPO), free thyroxine (FT4) and thyroid-stimulating hormone (TSH) in relation to ultrasound echogenicity

Ultrasound echogenicity	Anti-TPO U	FT4 (nmol/L)	TSH (mIU/L)
	mean ± SEM	mean ± SEM	mean ± SEM
Normal echogenicity (group A)	58.5 ± 18.4	14.6 ± 5.5	1.05 ± 0.34
Decreased echogenicity (group B)	339.3 ± 57.8*	10.1 ± 2.9*	5.04 ± 1.98*
Mildly decreased echogenicity (subgroup B1)	248 ± 45.9*	11.2 ± 3.4*	3.82 ± 2.12*
Significantly decreased echogenicity (subgroup B2)	670 ± 116.7*†	8.8 ± 3.8*	8.75 ± 3.36*†

***statistically significant difference in relation to the group A, ($p < 0.001$); †Statistically significant difference in relation to the group B1, ($p < 0.001$).**
SEM – standard error of mean.

Table 3

Number of patients according to the values of thyroid-stimulating hormone (TSH) and ultrasound echogenicity

Ultrasound echogenicity	TSH (< 4mIU/L) n (%)	TSH (4–10 mIU/L) n (%)	TSH > (10 mIU/L) n (%)
Normal echogenicity (group A)	420 (99)	4 (1)	0
Decreased echogenicity (group B)	174 (75)*	42 (181)*	16 (6.9)*
Mildly decreased echogenicity (subgroup B1)	162 (89.0)*	16 (8.8)*	4 (2.2)*
Significantly decreased echogenicity group B2	12 (24.0)*†	26 (52.0)*†	612 (24.0)*†

***Statistically significant difference in relation to the group A, $p < 0.001$; †Statistically significant difference in relation to the group B1, $p < 0.001$.**

Totally 20 (11%) examinees suffered from altered thyroid function. In the group with significantly decreased echogenicity the subclinical hypothyreoidism was found in 26 examinees, while the clinical hypothyreoidism was found in 12 examinees demonstrating that 38 (76%) examinees suffered from altered thyroid function.

There was a moderate negative correlation between anti-TPO and FT4 and high positive correlation between anti-TPO and TSH in the groups with reduced echogenicity. The results are shown in Table 4.

Table 4

Correlation of anti-thyroid peroxidase (TPO) with free thyroxine (FT4) and thyroid-stimulating hormone (TSH)

Hormones	Group A ρ	Group B ρ	Group B1 ρ	Group B2 ρ
FT4	0.09	-0.36	-0.32	-0.35
TSH	0.16	0.58*	0.52*	0.61*

ρ – Spearman's coefficient of correlation; * $p < 0.001$.

Discussion

Ultrasound diagnostics of thyroid gland diseases is generally accepted and indispensable in defining its morphology. In discovering thyroid gland disfunction, we primarily use the presence of characteristic symptoms and determination of thyroid hormone levels and TSH releasing hormone of pituitary gland. Undoubtedly, the majority of disfunctions are followed by the changed morphology, most commonly the increase – struma and/or nodule presence. Modifications of ultrasonographic characteristics of thyroid gland tissue can be present in its altered function. Decrease of ultrasound echogenicity can be one of the signs of altered thyroid function. Our results clearly speak in favor of ultrasound method of thyroid gland examination as an important method when there is a suspicion of its altered function. Decreased tissue echogenicity during the ultrasound screening is usually followed by an increase of thyroid antibodies and the change in its hormone level. In persons with normal echogenicity the presence of TPO and TG antibodies are found only in a minority of examinees, i.e., 8.5% and 10.4%, respectively that is followed by normal values of FT4 and TSH. With decreased echogenicity the percentage of persons with the presence of antibodies is significantly higher – 48.3% with anti-TPO increase and 41.4% with positive anti-TG. The differences were even more significant in the group with significantly decreased echogenicity – 88.0% and 80.0% examinees, respectively. Other authors also discovered that the persons with decreased thyroid gland echogenicity have significantly frequent increase of anti-TPO (30.6%) in relation to the persons with the normal ultrasound results (6.8%), that is, that the percentage of persons with decreased ultrasound echogenicity reaches 45.95% when antibodies are present, and only 12.4% when there is no increase in anti-TPO [7]. The increase in anti-TPO is six times more probable in case there is a decrease of thyroid gland echogenicity. It is shown that there was a significant correlation between the increase of anti-TPO and thyroide disfunction and that even in persons with TSH values of 2–4 mIU/L there is a significantly higher percentage of those with antibodies increase. The prevalence of TSH increase is almost ten times higher, not only in females, but also in males with the anti-TPO increase in relation to those with no increase [6]. Pedersen et al. [1] states that in the group with a decreased echogenicity the percentage of those with chronic autoimmune thyroiditis was 41%, while 30.6% are with increased anti-TPO, and even 46.8% with altered thyroid function [2]. The study that monitored the group of healthy medical workers over three years period found out that all those that evolved thyroid disfunction in this period suffered from decreased ultrasound echogenicity of thyroid gland at the beginning of the monitoring process [3]. The similar results are achieved by Marcocci et al. [8] who stated that all the persons with hypothyreoidism diagnosed within 18 months, were affected by the decreased thyroid gland echogenicity at the beginning of the monitoring process. An early detection of subclinical and clinical hypothyreoidism is important when having in mind that these are the persons with higher risk of atherosclerosis and cardiovascular disease incident as well as obesity [6]. In our study, in the group of examinees with the normal echogenicity we found only 4 (1%) cases of subclinical hypothyreoidism with TSH values of 4–10 mU/L. In the group with decreased echogenicity the percentage was significantly higher and there ware 58 (25%) patients in the whole group affected by sublinical (UZ 42) or clinical hypothyreoidism (UZ 16). Frequency of thyroid gland function decrease was particularly pronounced in the group with significantly decreased echogenicity; even in 76% of patients a disfunction was found in the sense of sublinical or clinical hypothyreoidism. Other authors also found higher frequency of thyroid gland hypoechogenicity in persons with higher TSH values, in relation to the group of per-

sons with normal values [3, 9–13]. It is stated that only 2.2% persons with normal ultrasound echogenicity suffer from subclinical hypothyreoidism. Comparison of various tests for thyroid dysfunction detection showed that the persons with normal echogenicity, normal anti-TPO and with no evidence of chronic autoimmune thyroiditis are 20% less endangered to be affected by thyroid disfunction.

Conclusion

The ultrasound screening of thyroid gland plays and important role in an early detection of thyroid disfunction, i.e., sublinical and clinical hypothyreoidism. Persons with uncharacteristic symptoms and signs and decreased ultrasound echogenicity of thyroid gland require more thorough endocrinological testing and determination of thyroid hormones level, TSH and thyroid antibodies. The testing results imply that the decreased ultrasound echogenicity represents the significant marker of altered thyroid gland function. In these persons we determined the high percentage of subclinical and clinical hypothyreoidism frequency. An early detection of subclinical and clinical hypothyreoidism is significant if keeping in mind that these persons are with higher risk of atherosclerosis and cardiovascular disease incident as well as obesity which emphasises the importance of ultrasound screening in everyday clinical practice.

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