Changes of Thyroidal Tc-99m Tetrofosmin Uptake and Wash-Out in Patients with Hashimoto's Thyroiditis

Hashimoto Tiroiditli Hastalarda Tiroitteki Tc-99m Tetrofosmin Tutulumu ve Atılımındaki Değişiklikler

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Geliş Tarihi/*Received:* 02.09.2008
Kabul Tarihi/*Accepted:* 21.01.2009

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ABSTRACT Objective: Our aim was to investigate the changes in Tc-99m tetrofosmin uptake and wash-out in the thyroid gland of normal volunteers and Hashimoto's thyroiditis (HT) patients with either euthyroidism or hypothyroidism. **Material and Methods:** Thirty-four patients with HT (10 hypothyroid and 24 euthyroid) and 10 euthyroid healthy volunteers were enrolled in the study. In all cases, thyroid stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3), anti-thyroid antibodies and thyroid volume were measured. Anterior thyroid images were acquired at 10, 30 and 120 min after intravenous injection of 740 MBq Tc-99m tetrofosmin. Thyroid/ background (T/B) ratios at 10, 30 and 120 min and wash-out indices (WI %) at 30 and 120 min were calculated. **Results:** In all groups, initial and late tetrofosmin T/B values did not differ from healthy control cases. At 120 min, the mean WI% of patients with hypothyroidism was significantly higher than that of volunteers; however this group is not statistically different from the euthyroid group. The value WI % at 120 min was significantly correlated with anti-Tg antibody levels (r= -0.673; p= 0.033). In the euthyroid group, both anti-TPO antibody levels and thyroid volume had significant correlations with the T/B ratios at 10, 30 and 120 min (r= 0.499, p= 0.013; r= 0.424, p= 0.039; r=0.528, p= 0.008 for Anti-TPO Antibody, and r= 0.577, p= 0.003; r= 0.606, p= 0.002; r= 0.645, p= 0.010, for thyroid volume, respectively). **Conclusion:** We can conclude that Tc-99m tetrofosmin uptake and wash-out kinetics in thyroid tissue may be changed with autoimmune thyrocyte destruction in HT.

Key Words: Technetium Tc 99m tetrofosmin; Hashimoto disease; radionuclide imaging

ÖZET Amaç: Amacımız ötirioidizm veya hipotiroidizmli Hashimoto Tiroiditli (HT) hastaların ve sağlıklı gönüllülerin tiroid bezindeki Tc-99m tetrofosmin tutulum ve atılımındaki değişiklikleri araştırmaktı. **Gereç ve Yöntemler:** Hashimoto Tiroiditli 34 hasta (10'u hipotiroid ve 24'ü ötiroid) ve 10 ötiroid sağlıklı gönüllü çalışmaya alındı. Tüm olguların tiroid stimule edici hormon (TSH), serbest tiroksin (FT4), serbest triiyodotironin (FT3), anti-tiroid antikor düzeyleri ve tiroid hacimleri ölçüldü. İntravenöz olarak 740 MBq Tc-99m tetrofosmin enjeksiyonundan sonra 10, 30 ve 120 dakikalarda anterior tiroid görüntüleri alındı. Bu görüntülerden 10, 30, 120 dk tiroid/zemin aktivite (T/B) oranları ve 30 ve 120 dakikadaki "wash-out" indeksleri (%WI) hesaplandı. **Bulgular:** Tüm gruplarda, başlangıç ve geç tetrofosmin T/B değerleri sağlıklı kontrol olgularından farklılık göstermedi. Hipotiroidizmli hastaların 120.dk'daki ortalama %WI'i gönüllülerden anlamlı şekilde daha yüksekti, buna karşın ötiroid hastalardan anlamlı farklılık göstermedi. Yüzyirminci dakika %WI değeri anti-Tg antikor düzeyi ile anlamlı negatif korelasyon içinde idi (r= -0.673; p= 0.033). Ötiroid grupta, anti-TPO antikor düzeyleri ve tiroid hacmi 10, 30 ve 120 dk T/B oranları ile anlamlı pozitif korelasyona sahipti (Anti-TPO Ab için sırası ile r= 0.499, p= 0.013; r= 0.424, p= 0.039; r= 0.528, p= 0.008 ve tiroid volümü için sırası ile r= 0.577, p= 0.003; r= 0.606, p= 0.002; r= 0.645, p= 0.010). **Sonuç:** Tiroid bezindeki Tc-99m tetrofosmin tutulumu ve atılımı kinetiklerinin HT deki otoimmün tirosit hasarına ile değişebileceği sonucuna varabiliriz.

Anahtar Kelimeler: Tc-99m tetrofosmin; Hashimoto tiroiditi; sintigrafi

Turkiye Klinikleri J Med Sci 2010;30(1):115-22

Hashimoto's thyroiditis (HT) (also known as chronic lymphocytic thyroiditis or chronic autoimmune thyroiditis) is a widely-seen disease, particularly in young women in Aegean region of Turkey. The course of the disease varies and patients may have normal thyroid function or hypothyroidism at the time of initial diagnosis.[1-3]

Tc-99m tetrofosmin (Tc-99m 1,2-bis[bis(2-ethoxyethyl) phosphino]ethane) is a myocardial perfusion imaging radiotracer such as Tc-99m methoxyisobutylisonitrile (Tc-99m MIBI) or Tl-201. Those three radiopharmaceuticals are also used as tumor or parathyroid imaging agents.[4,5] The increased uptake of Tc-99m MIBI or Tl-201 in the thyroid gland has been demonstrated in patients with autoimmune thyroid diseases (Graves disease and HT).[6,7] However, we have hardly any information regarding thyroid uptake of Tc-99m tetrofosmin in patients with chronic autoimmune thyroiditis; except only two published case reports. In the first case with HT, Kresnik et al[8] did not find any increased Tc-99m tetrofosmin uptake or retention in their patient, whereas Kao et al[9] observed an increased Tc-99m tetrofosmin uptake in their patients.

In this study, we investigated the changes in Tc-99m tetrofosmin uptake and wash-out in the thyroid glands of normal volunteers and in patients with euthyroid or hypothyroid HT.

MATERIAL AND METHODS

Thirty-four patients with a previous diagnosis of HT (4 M/ 30 F; mean age ± SD= 43 ± 13 years) and 10 euthyroid volunteers (3 M/ 7 F; mean age ± SD= 53 ± 14 years) were studied. Ages of patients with HT were different from the ages of volunteers. This prospective study was approved by the Faculty Ethical Committee and informed consent was obtained from all participants.

The HT diagnosis was made on the basis of history and clinical examination, high anti-thyroid antibody levels [Anti-thyroglobuline (Anti-Tg)> 40 IU/ml; Anti-thyroid peroxidase (Anti-TPO)> 35 IU/ml by electrochemical immunoassay (Immulite 2000, USA)], abnormal findings with thyroid ultrasonography (TUS) such as diffuse hypoechogenity with pseudonodular changes and parenchymal irregularity, and heterogeneous radiopharmaceutical uptake in Tc-99m pertechnetate thyroid scanning. Cytological evaluation was not performed during this study.

Patients were grouped as hypothyroid (n= 10) and euthyroid (n= 24), based on their thyroid stimulating hormone (TSH) levels. Thyroid hormone replacement therapy of patients with hypothyroidism was not stopped during study.

The control group consisted of the cases with no history of a new or previous diagnosis of goiter, any kind of thyroiditis, abnormalities in thyroid function tests or a systemic disorder. All volunteers were chosen among people working in our hospital.

Cases with a history of thyroidectomy or parathyroidectomy, those with palpable thyroid nodules and/or TUS were excluded from the study group.

All patients and control cases underwent to TUS and Tc-99m tetrofosmin thyroid scintigraphy.

Thyroid volume was measured using a high-resolution real-time ultrasound equipped by 7.5 MHz linear probe. Volumetric measurements were obtained according to method of Ivanac et al.[10] Thyroid volumes were calculated according to the spherical ellipsoid formula: volume = $\pi/6$ x anteroposterior diameter (cm) x width (cm) x length (cm). In each subject, measurements were performed by the same physician. The normal thyroid volume determined by ultrasonography was accepted as 11.1 ± 3.2 ml for females (upper limit = 20.2 ml), 13.7 ± 3.4 ml for males (upper limit= 22.4 ml) according to the report of Erdogan et al.[11]

All cases were subjected to Tc-99m tetrofosmin scintigraphy. A CamStar AC/T gamma camera (GE, Milwaukee, Wisc., USA) equipped by a LEAP collimator was used for image acquisition. Planar anterior neck images with a 256 × 256 matrix and zoom of 1.33 were acquired at 10 min, 30 min and

120 min for a 10 minute period following intravenous injection of Tc-99m tetrofosmin (MyoviewÔ; Nycomed Amersham plc., Bucks, UK) at a dose of 740 MBq (20 mCi).

Regions of interest (ROIs) were drawn over the whole thyroid gland and neck on each image. The net count of the thyroid gland was calculated by subtracting the neck counts from the thyroid counts. Afterwards, thyroid/ background ratios on the 10 min, 30 min and 120 min images, and washout indices (WI %) for the 30 min and 120 min images were calculated using the formula given below;

WI %= [(early net thyroid cts-late net thyroid cts) x 100/early net thyroid cts]

Data were expressed as mean ± standard error. A Kruskal-Wallis test was used to calculate the difference between the means of the three groups. The significance of the means in Kruskal-Wallis test was verified by the Mann-Whitney U test with Bonferroni correction to protect against Type I error due to multiple comparisons. Spearman's correlation analysis was used to evaluate the correlation of Tc-99m tetrofosmin uptake and washout kinetics with ultrasonographic thyroid volume and serological tests (anti-thyroid antibodies) for each group. The significance level was set at $p \leq 0.05$.

RESULTS

Early and late thyroid to background uptake (T/B) ratios were very similar for each group (Table 1). There was no significant difference between the ratios of patients with each type of clinical status and the healthy control cases (Figure 1). However, in each group, the T/B ratios showed significant differences from the 10 min to the 120 min time points ($p< 0.005$).

The difference among the mean wash-out rates of all the groups at 120 min was statistically significant ($p< 0.05$). Tc-99m tetrofosmin WI % at 120 min. (71% ± 3%) in the hypothyroid group was significantly higher than that of healthy volunteers (57% ± 3%) ($p< 0.05$). Although the hypothyroid group had rapid clearances at 30 min and 120 min (29% ± 3% and 71% ± 3%, respectively) compared to the euthyroid group (26% ± 1% and 64% ± 2%, respectively), statistically significant differences were not detected (Table 1, Figure 2) ($p> 0.05$).

We performed correlation analysis for each parameter. In the euthyroid group, the anti-TPO antibody levels had significantly positive correlations with the 10 min T/B ratios ($r= 0.499$; $p= 0.013$), 30 min T/B ratios ($r= 0.424$; $p= 0.039$) and 120 min T/B ratios ($r= 0.528$; $p= 0.008$). In the hypothyroid group, no correlations were detected between anti-TPO antibody levels and T/B ratios. In

TABLE 1: Results of laboratory, ultrasonographic and scintigraphic parameters of the volunteers and the patients (Values are presented as mean ± standard error).

	Volunteers	Euthyroidism	Hypothyroidism	p values*
N	10	24	10	
Age (years)	53 ± 5	40 ± 2	47 ± 5	**0.041*** **
Anti-Tg (< 40 IU/ml)	< 20	154.25 ± 49.08	255.09 ± 66.03	**0.034****
Anti-TPOAb (< 35 IU/ml)	< 10	291.78 ± 78.11	940.53 ± 325.64	**0.038****
Thyroid volume (mm^3)	16.40 ± 2.1	15.57 ± 2.9	17.52 ± 11.52	0,761*
10 min T/B ratio	2.25 ± 0.17	2.40 ± 0.12	2.41 ± 0.27	0.976*
30 min T/B ratio	2.02 ± 0.17	2.12 ± 0.11	2.00 ± 0.16	0.914*
120 min T/B ratio	1.72 ± 0.12	1.67 ± 0.69	1.48 ± 0.09	0.248*
30 min WI %	26 ± 1	26 ± 1	29 ± 3	0.582*
120 min WI %	57 ± 3	64 ± 2	71 ± 3	**0.042***

* Kruskal-Wallis Test.

** Mann-Whitney U test was used for the comparisons between hypothyroid group and euthyroid group, could not be compared with volunteers.

*** Mann-Whitney U test was used for the comparisons between 34 Hashimoto' thyroiditis patients and 10 volunteers.

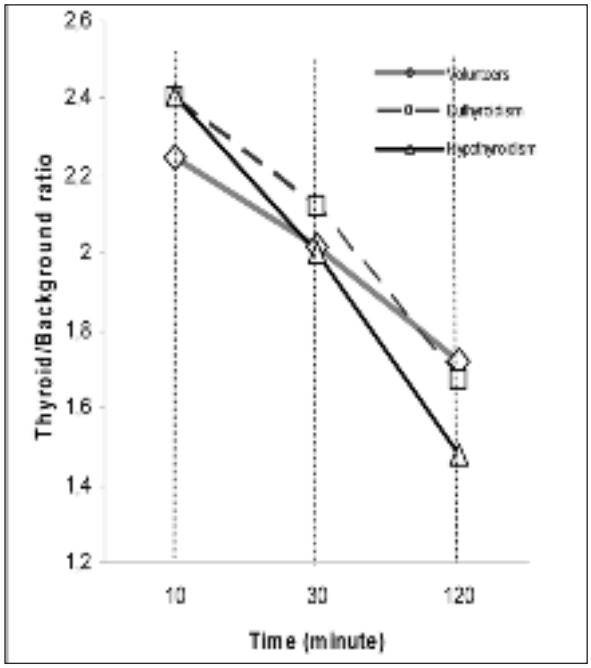

FIGURE 1: Thyroid to background ratios of the three groups showed a decrease from 10 min to 120 min. Although the decline of the hypothyroid group is more prominent than the other two groups, the differences among the three groups are not statistically significant.

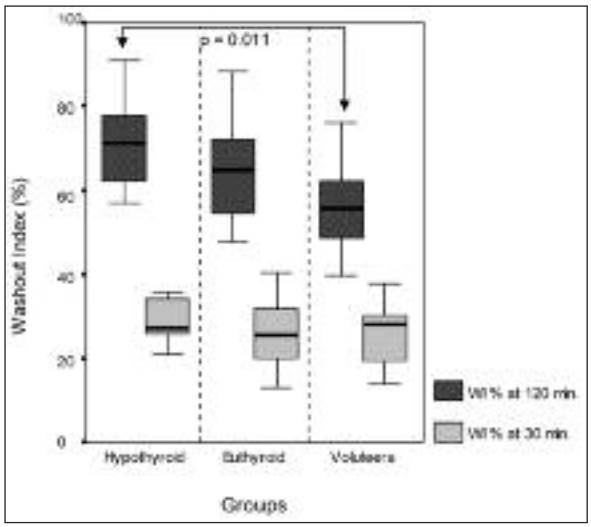

FIGURE 2: Comparison of the wash-out indices of the three groups shows a significant difference at 120 minutes (p= 0.042 by Kruskal-Wallis Test). The hypothyroid group exhibits a more rapid clearance at 120 min than the volunteer group (p= 0.001 by Mann-Whitney U test) (line with arrow heads).

both patient groups, we did not detect any correlations between anti-Tg antibody levels and T/B ratios at the three time points.

Thyroid volumes were normal (26 patients) or hypertrophic (8 patients). In all patients with HT, the thyroid volume had significant positive correlations with T/B ratios (Table 2). The mean thyroid volume in euthyroid group was observed as a bit smaller than other two groups (Table 1). In this group, the thyroid volume had significant positive correlations with the 10 min T/B ratios (r= 0.577; p= 0.003), 30 min T/B ratios (r= 0.606; p= 0.002) and 120 min T/B ratios (r= 0.645; p= 0.001). No correlation was detected between the thyroid volume and the T/B ratios in the hypothyroid group. We did not find any relationship between thyroid volume and anti-thyroid antibody levels in both groups (Table 2).

DISCUSSION

Only two cases in the literature have addressed the thyroid Tc-99m tetrofosmin biokinetics in HT.[8,9] It has been reported that the kinetics of Tc-99m Tetrofosmin in thyroid tissue and parathyroid lesions are different from Tc-99m methoxy isobutyl isonitrile (MIBI) kinetics.[12,13] In many studies, the images were obtained at 30 and 120 min after injection of radiopharmaceuticals in a dual phase Tc-99m MIBI study, and, at 10 and 30 min post-injection in a dual phase Tc-99m tetrofosmin study.[12-18] These acquisition time points are widely used in parathyroid pathologies[15,18-21] and thyroiditis studies.[9,22,23]

In the present study, we evaluated the uptake of thyroid Tc-99m tetrofosmin in patients with HT and compared them with volunteers. We used three imaging time points of 10 min, 30 min and 120 min. Tetrofosmin uptake ratios at all scanning time points in HT groups were similar with controls. Thyroid to background ratios calculated according to these imaging times were almost same with the results of Giordano et al,[24] except for the result of the 120 minute T/B of the hypothyroid group (Table 1). In the hypothyroid group, the 120 minute T/B (1.48 ± 0.09) was markedly lower than the result from Giordano's study (1.65 ± 0.58). This may be related to the healthy persons in their study group which is different from our group composing of hypothyroid patients. As mentioned

TABLE 2: The correlative analysis of Tc-99m tetrofosmin T/B ratios and WI% values with anti-TPO antibody, anti-Tg antibody and US volume in patients with Hashimoto's thyroiditis.

		T/B10min	T/B 30 min	T/B 120 min	WI % 30 dk	WI % 120 dk
All patients	N	34	34	34	34	34
Anti-TPO	r	0.261	0.235	0.195	-0.108	0.01
	p	0.137	0.182	0.269	0,544	0.954
Anti-Tg	r	0.120	0.056	0.380	0.043	0.023
	p	0.499	0.753	0.832	0.809	0.896
US volume	r	**0.436**	**0.516**	**0.534**	-0.329	-0.260
	p	**0.010**	**0.002**	**0.001**	0.057	0.138
Euthyroid patients	N	24	24	24	24	24
Anti-TPO	r	**0.499**	**0.424**	**0.528**	-0.219	-0.076
	p	**0.013**	**0.039**	**0.008**	0.304	0.723
Anti-Tg	r	0.250	0.210	0.017	0.041	0.030
	p	0.239	0.325	0.939	0.851	0.890
US volume	r	**0.577**	**0.606**	**0.645**	-0.587	-0.374
	p	**0.003**	**0.002**	**0.010**	0.003	0.072
Hypothyroid patients	N	10	10	10	10	10
Anti-TPO	r	-0.224	-0.006	-0.176	-0.261	0.139
	p	0.533	0.987	0.627	0.467	0.701
Anti-Tg	r	-0.273	0.067	0.345	-0.539	-0.673
	p	0.446	0.855	0.328	0.108	0.033
US volume	r	-0.042	0.115	0.333	0.164	-0.261
	p	0.907	0.751	0.347	0.651	0.467

US: Ultrasonography, T/B: Thyroid/background.

before, T/B ratios at 120 min. in the euthyroid (1.67 ± 0.69) and the control (1.72 ± 0.12) groups were the same as their results. Therefore, we supposed that the number of functional thyroid cells is one of the important factors effecting tetrofosmin kinetics in the thyroid tissue. Because the early tetrofosmin uptake into thyroid gland is the reflection of blood pool activity, early tetrofosmin uptake is not significantly different between the hypothyroid patients and the volunteers. As the late tetrofosmin uptake into thyroid gland shows the number of functional thyroid cells, lower, uptake compared to the volunteers may be associated with degree of severity of the inflammatory or cytotoxic processes in the thyroid glands. The significant moderate correlation between thyroid volume and T/B ratios in all the patients with HT (Table 2) supports to this idea. Thus, late tetrofosmin uptake decreases in hypothyroid group even though thyroid volume measurements are not different from the others. Probably, inflammatory reaction may affect result in reduced tetrofosmin uptake in hypothyroid patients due to severe oedema.

We also detected changes in wash-out parameters in patients with hypothyroidism. ^{99m}Tc-tetrofosmin WI% at 120 minutes in the hypothyroid group was significantly higher than that of healthy volunteers (p= 0.011). A mean 71% of tetrofosmine was washed out from the thyroid gland until the 120 minute time point. Although the hypothyroid group showed faster clearances at 30 min and 120 min compared with the euthyroid group, statistically significant differences were not detected (Table 1, Figure 2). ^{99m}Tc-tetrofosmin 120 min WI% values of the patients with HT were higher than those of volunteers. However, the difference among the mean thyroid volume of the groups was not statistically significant (p> 0.05). In this study, thyroid hormone replacement therapy of patients with hypothyroidism was not ceased during study. Because of that, we assume that the basal metabolism rates in patient groups were similar to those of

the healthy cases, and the fibrosis of thyroid effecting the perfusion of thyrocytes did not develop in hypothyroid patients. Thus, we suggest that the changes in^{99m} Tc-tetrofosmin kinetics in thyroid tissue parallels the degree of thyrocyte destruction in HT. Tetrofosmin is a perfusion agent,[25] and is an indicator of cell viability.[26,27] Kresnik et al[8] reported decreased tetrofosmin uptake in patients with degenerative goiter and HT in a late scan obtained at 1 h after injection. In other study, Younes et al[25] showed that the mechanism of tetrofosmin uptake was dependent on the amount of mitochondrial proteins using cell-based systems. Based on the data from Younes's report,[25] Kresnik et al[8] suggested that the decrease or loss of uptake capability in thyroid tissue was due to degenerative changes.

This destructive process that affects thyroidal tetrofosmin kinetics depends on autoimmune pathology. We detected that the anti-Tg and anti-TPO antibodies were markedly high in the hypothyroid group when compared to the euthyroid group ($p= 0.034$ and $p= 0.038$, respectively). In the euthyroid group, the anti-Tg antibody levels had significantly positive correlations with 10 min, 30 min and 120 min T/B ratios. Similarly, thyroid volumes also had significantly positive correlations with 10 min, 30 min and 120 min T/B ratios in euthyroid patients.

These findings may be the indirect evidence of active inflammatory process, because no correlation was observed between tetrofosmine T/B ratios and thyroid volume in hypothyroid patients. In the euthyroid group, the positive correlations of Tc-99m tetrofosmin uptake with anti-TPO antibody levels and thyroid volumes suggested the active inflammatory process. Our findings support the results of Bogner et al[28] They reported that microsomal antibodies were responsible for the cytotoxic effect, whereas thyroglobulin antibodies did not mediate cytotoxicity. On the other hand, similar to the results of Rieu et al,[29] we did not find any relationship between thyroid volume and anti-TPO antibody in euthyroid or hypothyroid patients.

It has already been reported that autoimmune reactions can augment follicular cell damage.[30] A few studies recently published have shown that the high expression of key molecules (such as fas, fas ligand) that regulate cell death in HT promote thyrocyte apoptosis, tissue damage and a gradual reduction in thyrocyte numbers, leading to hypothyroidism.[31-33] There are few reports about the use of Tc-99m tetrofosmin in diagnosing apoptosis. Sükan et al[26] showed that significantly increased Tc-99m tetrofosmin uptake into the bone marrow was well correlated with CD95, an inhibitor of apoptosis in patients with acute leukemia. Wakasugi et al[27] reported a case of malignant pheochromocytoma that showed early intense uptake and immediate rapid wash-out of Tc-99m tetrofosmin. They also characterized overexpression of the anti-apoptotic molecule Bcl-2 in this case, which was refractory to I-131 MIBG therapy.[27] Salmaso et al[34] reported that they did not observe any significant apoptosis in lymphocytes infiltrating HT glands, suggesting that the HT microenvironment did not promote lymphocyte apoptosis. The expression of the anti-apoptotic molecule Bcl-2 is increased in HT lymphocytes and reduced in thyrocytes, and the regulation of Fas/FasL/Bcl-2 expression in HT can promote thyrocyte apoptosis via homophilic Fas-FasL interactions, and a gradual reduction in thyrocyte numbers leads to hypothyroidism.[35] Based on the results of these studies, we deduce that up-regulation of Fas and FasL and down-regulation of Bcl-2 protein appear to trigger apoptosis in thyroid follicular cells in HT.

Although there are no reports about tetrofosmin kinetics and apoptosis in HT, we can hypothesise a possible connection between them based on the results of the previous studies mentioned above. The similarity in early T/B ratios for the three groups (Table 1) suggests a reduction in blood flow and membrane electrical gradient. The increased thyroidal wash-out of tetrofosmin at 120 minutes in patients with HT is probably related to thyrocyte apoptosis. Therefore, tetrofosmin scanning appears to be a promising method to detect apoptosis in thyroid tissue. Nevertheless, since we did not perform fine-needle aspiration biopsy in our patients, we could not estimate the extent of apoptosis. Therefore, we cannot say that apoptosis

is solely responsible for increased wash-out of tetrofosmin, however it may change tetrofosmin kinetics along with other cellular mechanisms, such as blood flow rate, metabolic status and membrane integrity in thyrocytes.

As a conclusion, our findings show that the increased 120 min wash-out index of ^{99m} Tc-tetrofosmin, as a viability marker which may be related to autoimmune cytotoxic processes. In addition, we can say that the uptake and wash-out of ^{99m} Tc-tetrofosmin in thyroid tissue in HT patients change with the progression of disease. It needs further studies to define the importance of regulating cell death and the role of ^{99m} Tc-tetrofosmin in the determination of apoptosis in autoimmune thyroid disorders.

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