Thyroid functions after contrast agent administration for coronary angiography: a prospective observational study in euthyroid patients

Koroner anjiyografi amacıyla kontrast madde verildikten sonra tiroid fonksiyonları: Ötiroid hastalarda prospektif bir gözlemsel çalışma

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ABSTRACT

Objective: This study aims to investigate long-term effects of iodinated radiographic contrast media used for coronary angiography (CAG) on the thyroid function in euthyroid patients.
Methods: In a prospective observational cohort study, nonionic iodinated contrast material was electively used in 101 patients for coronary angiography. The patients were recruited without age restrictions and, at baseline, all had normal levels of free triiodothyronine (FT3), free thyroxine (FT4) and thyrotropin (TSH). The morphology of the thyroid was evaluated by thyroid ultrasonography (USG). Four and eight weeks after CAG, serum TSH, FT3 and FT4 levels were assessed.
Results: Compared to a mean baseline level of 1.49 (25%-75%, range 13-2.21), follow-up TSH levels decreased significantly to 1.45 (25%-75%, range 1.98-0.92, p=0.017) and 1.40 (25%-75%, range 1.89-0.87, p=0.003) at 4 weeks and 8 weeks, respectively (p=0.008). No significant diffe-rence was observed in TSH levels between the 4th and 8th weeks (p=0.833).
Conclusion: Iodinated radiographic contrast agents may cause subclinical hyperthyroidism in euthyroid patients undergoing CAG.
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Key words: Contrast media, function tests, thyroid, coronary angiography

ÖZET

Amaç: Bu çalışma ötiroid hastalarda koroner anjiyografi için kullanılan radyolojik iyotlu kontrast maddelerin uzun dönemde tiroid fonksiyonlarına etkisini araştırmak amacıyla yapıldı.
Yöntemler: Elektif şartlarda koroner anjiyografi amacıyla noniyonik iyotlu kontrast madde kullanılan 101 hastada prospektif gözlemsel kohort çalışması yapıldı. Çalışmaya alınan tüm hastaların serbest triiodotironin (sT3), serbest tiroxin (sT4), bazal tirotropin (TSH) değerleri normaldi ve yaş sınırlaması yapılmadı. Tiroid ultrasonografi (USG) yapılarak tiroid morfolojisi değerlendirildi. KAG işleminden 4 hafta ve 8 hafta sonra hastaların serum TSH, sT3, sT4 değerleri kontrol edildi.
Bulgular: TSH bazalda 1.49 (%25-%75;13-2.21); 4.haftada 1.45 (%25-%75; 0.92-1.98) ve 8.haftada 1.40 (%25-%75; 0.87-1.89) olarak saptanmış olup; takipler arası değişim istatistiksel olarak anlamlı bulunmuştur (p=0.008). Bazal TSH düzeylerine göre 4. haftada (p=0.017) ve 8. haftada (p=0.003) istatistiksel olarak anlamlı düşüşler gözlenirken; 4. hafta ile 8. hafta TSH düzeyleri arasında anlamlı değişim gözlenmedi (p=0.833).
Sonuç: Ötiroid hastalarda koroner anjiyografi amacıyla iyotlu radyolojik kontrast maddelerin kullanılması subklinik hipertiroidizme neden olabilir. *(Anadolu Kardiyol Derg 2013; 13: 363-9)*
Anahtar kelimeler: Kontrast madde, tiroid fonksiyon testleri, koroner anjiyografi

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Introduction

Iodinated contrast media (ICM) is among the most prescribed drugs in today's modern medicine (1). The use of ICM in clinical cardiology and radiology, where the catheterization procedure is the major diagnostic and therapeutic application, is associated with contrast nephropathy, allergic reactions, cerebrovascular accidents, etc., and an increased incidence of complications (2). Besides contrast nephropathy, ICM has a significant effect on thyroid function (3). A 200 mL dose of contrast medium containing 35µ/mL provides 7.000 µg free iodide, equivalent to 45 times the recommended daily intake (4). Adult age group (14-≥70 age) The average daily iodine requirement is 95 mg/day, with a dietary allowance of 150 mg/day (5). These sudden high doses can disrupt the regulation of iodide and thyroid hormone and further cause hyperthyroidism (jod Basedow) (6). Iodine not only plays a significant role in thyroid hormone synthesis but also modulates the thyroid function. As a response to an acute iodine load, the normal thyroid transiently decreases the synthesis of thyroid hormones but then recovers due to a decrease in the thyroid sodium/iodide symporter, resulting a decrease in iodine transport into the thyroid and resumption of normal thyroid hormone synthesis (7). It has been observed that the thyroid function appears to be in the normal range following the use of an iodide load in individuals with normal thyroid glands (8).

Iodine-induced hyperthyroidism has been reported in patients with a variety of underlying thyroid diseases, but primarily occurs in individuals with nodular thyroid disease (9, 10). Martin et al. showed development of hyperthyroidism after the use of contrast agents (11). Another study showed that, following the use of contrast agent, euthyroid patients developed subclinical hypothyroidism (12). Moreover, Marraccini et al. (13) not only found that thyroid dysfunction in patients undergoing coronary angiography, but it was also an independent risk factor for overall mortality and major cardiovascular events.

The purpose of this study was to determine the effect of non-ionic contrast agents containing iodine in euthyroid patients and to evaluate the morphology of the thyroid gland and thyroid auto-antibodies to investigate the possible negative long-term effects on thyroid function.

Methods

Study design

This prospective observational cohort study was carried out between September and January 2010 in İstanbul, Turkey.

Study population

A total of 101 euthyroid patients (30 women, 71 men; age range: 20 to 85 years) undergoing elective coronary angiography were selectively included in the study.

Patients who had been subject to contrast agent over the last 6 months, those using iodine-containing agents, patients with arrhythmia, known coronary artery disease and those with known thyroid disease were excluded. Baseline thyroid function tests were normal in all the subjects, with free triiodothyronine (fT3), free thyroxine (fT4) and thyroid stimulating hormone (TSH) values being in the range of 2.3-4.5 pg/mL, 0.75-2 ng/dL and 0.55-4.78 µIU/mL, respectively. Subjects with abnormal results for thyroid tests were excluded. The study protocol was approved by the Ethics committee of the institution. All patients read and signed the volunteered experimental information form.

Study protocol

Blood samples were drawn from patients an hour before injection of contrast materialto measure baseline serum fT3, fT4, TSH, thyroid peroxidase antibody (anti-TPO) and thyroglobulin antibody (antiTG) levels. Morphology of the thyroid gland was evaluated by an expert radiologist prior to the injection of contrast material. Following coronary angiography with contrast agents, levels of serum T3, T4 and TSH were measured at 4 and 8 weeks.

Study variables

The demographic variables were age and gender and laboratory variables were FT3, FT4, TSH and thyroid volume.

Coronary angiography and iodine contrast media

Iodine amount per kilogram weight of the patients was calculated by estimating iodine amount in contrast agent preparations that were used. The mean amount of iodine given with contrast agent before coronary angiography was calculated as 0.35 g/kg.

Coronary angiography was carried out using different amounts of Ultravist(R) (370 mg iodine/mL; Schering AG, Berlin, Germany).

Thyroid function tests

The results of baseline thyroid function tests were normal in all subjects with ranges of free fT3, fT4 and TSH values as 2.3-4.5 pg/mL, 0.75-2 ng/dL, and 0.55-4.78 µIU/mL, respectively. An anti-TPO positive result was considered to be >50 IU/mL, and an antiTG negative result was considered to be <150 IU/mL. Serum TSH, FT3, FT4 levels were measured on an automated analyzer immunochemoluminescent equipment (Siemens ADVIA Centaur ® XP Immunoassay System, Germany). Serum antiTG and anti-TPO levels were measured by the enzyme immunoassay method (AIDA kit, GmbH / Germany).

Subclinical hyperthyroidism was diagnosed on the basis of suppressed TSH and normal fT4 values (14). Overt hyperthyroidism was defined as the presence of elevated fT4 and suppressed TSH levels, in combination with clinical signs. Overt hypothyroidism was defined on the basis of elevated TSH with lowered fT4. Subclinical hypothyroidism was diagnosed when TSH was elevated and fT4 was normal.

Ultrasound evaluation of thyroid gland

The morphology of the thyroid gland was assessed by the same radiologist prior to injection of contrast material, using a

10-MHz linear probe (5 Logic Pro, GE Medical Systems, WI, USA). For volume estimation, the sizes of both lobes were considered separately and their volumes were calculated by the ellipsoid formula (V=AxBxCx0.523; V=volume; A, B, C: 3 separate orthogonal sizes of the lobe) and total thyroid volume was estimated by summing of these two values (15). Enlargement of the thyroid gland was defined as a volume exceeding 18 mL in females and 25 mL in males (16). Nodular lesions measuring ≥3 mm on ultrasonography were recorded as thyroid nodules.

Statistical analysis

Data were analyzed using the Number Cruncher Statistical System (NCSS) 2007 and Power Analysis and Sample Size (PASS) 2008 Statistical Software (Utah, USA). In addition to descriptive statistical methods for quantitative variables (mean, standard deviation), repeated measures ANOVA test was used to evaluate parameters with normal distribution and Bonferroni test was used for post-hoc comparisons. For parameters without normal distribution, the Mann-Whitney U-test was used for inter-group comparisons and Friedman test and Wilcoxon sign test were used for intra-group comparisons. The Spearman correlation analysis was used to evaluate relationships between the parameters. For comparison of qualitative data, the Fisher's exact test was used. Significance level was set at $p<0.05$. The Mc-Nemar test and Cohen's Kappa compliance test were used in qualitative comparisons of the data.

Table 1. Distribution of age

	Min-Max	Mean±SD
Age, years	20-85	59.50±12.23
	n	%
20-34	4	4.0
35-49	13	12.9
50-64	47	46.5
≥65	37	36.6

SD - standard deviation

Table 2. Evaluation of TSH levels

	TSH (µ/UlmL)	
	Median	25%-75% percentile
Baseline	1.49	1.13-2.21
4th week	1.45	0.92-1.98
8th week	1.40	0.87-1.89
*p	0.008**	
+Baseline-4th week	0.017	
+Baseline-8th week	0.003	
+4. week-8. week	0.833	

*Friedman test , + Wilcoxon Signed Rank Test
TSH - thyroid - stimulating hormone
Baseline, before the administration of the contrast agent, levels of serum free T3 and free T4 of patients.
4 week - levels of serum free T3 and free T4 of patients 4 weeks after the administration of the contrast agent.
8 week - levels of serum free T3 and free T4 of patients 8 weeks after the administration of the contrast agent.

Results

The mean age of the patients was 59.5±12.2 years (range 20-85 years). Table 1 shows age distribution of the entire group.

Prior to the injection of contrast agent, TSH, fT4 and fT3 values were all in normal ranges with 0.56-4.50 µIU/mL, 0.83-1.60 ng/dL, and 2.31-4.21 pg/mL, respectively.

The median basal TSH level was 1.49 µIU/mL (25-75% percentile, 1.13 to 2.21). At 4 weeks, the median TSH level was 1.45 µIU/mL (25-75% percentile, 0.92 to 1.98), with seven patients (6.9%) having a TSH level below the normal range (subclinical hyperthyroidism) ($p<0.01$). At 8 weeks, the median TSH level was 1.40 µIU/mL (25-75% percentile, 0.87 to 1.89) with six patients (5.9%) having subclinical hyperthyroidism ($p<0.01$) (Table 2). None of the patients developed overt or subclinical hypothyroidism during the study period.

Compared to baseline, serum TSH levels showed significant decreases at 4 and 8 weeks ($p<0.05$ and $p<0.01$), whereas this decrease was not significant forweeks 4 and 8 ($p>0.05$).

Free T4 levels ranged between 1.80 and 0.83 ng/dL at week 4 and between 1.93 and 0.90 ng/dL at week 8, all being within normal limits.

Free T3 levels ranged between 4.21 and 2.13 pg/mL at week 4 and between 4.67 and 1.96 pg/mL at week 8 .No statistically significant change was observed in fT4 and fT3 levels at weeks 4 and 8 compared to the baseline levels ($p>0.05$) (Table 3). In the patients over age of 65, no statistically significant change was determined between follow-up measurements of TSH ($p<0,05$). Although the increase (median value was high but range interval

Table 3. Distribution of free thyroxine (fT4) levels and free triiodothyronine (fT3) levels.

	Free T3 (pg/mL)		Free T4 (ng/dL)	
	Mean	SD	Mean	SD
Baseline	3.05	0.36	1.14	0.16
4th week	3.09	0.39	1.17	0.17
8th week	3.09	0.42	1.16	0.17
*p	0.116		0.136	
+Baseline-4th week	0.075		0.133	
+Baseline-8th week	0.199		0.258	
+4. week-8th week	0.930		0.664	

*ANOVA for repeated measures test + posthoc Bonferroni test
Baseline, before the administration of the contrast agent, levels of serum free T3 and free T4 of patients.
4 week - levels of serum free T3 and free T4 of patients 4 weeks after the administration of the contrast agent.
8 week - levels of serum free T3 and free T4 of patients 8 weeks after the administration of the contrast agent.

Table 4. Assessment of week 4 and week 8 TSH results according to age criteria

TSH, µ/UlmL	Age, years		
	<65 years (n=64)	≥65 years (n=37)	
	Median (25%-75%)	Median (25%-75%)	°p
Baseline	1.57 (1.18-2.29)	1.25 (1.01-1.83)	0.077
4th week	1.54 (1.01-1.99)	1.37 (0.74-2.07)	0.245
8th week	1.44 (0.90-2.01)	1.35 (0.84-1.71)	0.292
*p	0.026	0.042	
+Baseline-4th week	0.030	0.316	
+Baseline-8th week	0.022	0.045	
+4th week-8th week	0.512	0.689	

°Mann Whitney U test, *Friedman Test , +Wilcoxon Signed Rank test

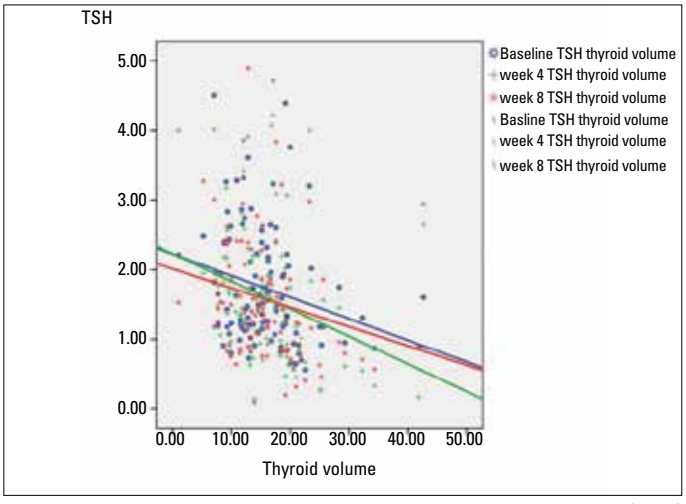

Figure 1. The relation between thyroid stimulating hormone (TSH) levels and thyroid volume

was wide) observed at week 4 compared to the baseline levels was not found to be statistically significant in our investigation (p> 0.05), the change observed at week 8 compared to the baseline levels was found to be reasonably meaningful (p <0.05) (Table 4).

There were 4 (4%) anti-TPO positive patients and 97 (96%) anti-TPO negative patients; and there were 2 (2%) antiTG positive and 99 (98%) antiTG negative patients. No statistically significant correlation was found between antiTG levels and TSH levels at baseline and weeks 4 and 8 (p>0.05). Mean thyroid volume ranged between 0.99 and 42.68 mL. Mean thyroid volume was 15.14±7.67 mL in women with thyroid volume being large in 8 (26.7%) women, while it was 16.28±6.51 mL in men with thyroid volume being large in 6 (8.5%) men. Discordance was statistically observed between the thyroid volume and TSH on week 4 (p>0.05). While 84.2% of patients were identified by both measurements as normal, 5% of the patients have large volume thyroid and low values of TSH levels. Non-random compliance between the two measurements (Cohen Kappa=0.423) was found to be 42.3%. There was a close relationship between the thyroid volume and TSH levels at 8 weeks (p>0,05).

Table 5. Assessment of week 4 and week 8 TSH results according to thyroid volume criteria

TSH, µ/UlmL		Thyroid volume		
		Normal, n (%)	Large, n (%)	*p
4th week	Normal	85 (84.2)	9 (8.9)	0.065
	Low	2 (2.0)	5 (5.0)	
8th week	Normal	83 (82.2)	12 (11.9)	0.077
	Low	4 (4.0)	2 (2.0)	

*McNemar test

TSH (µ/Ulml) Thyroid - stimulating hormone, range (0.55-4.78)

Table 6. Assessment of week 4 and week 8 TSH results according to nodule presence criteria

TSH, µ/UlmL		Thyroid Nodule		
		Present; n (%)	Absent; n (%)	*p
4th week	Normal	49 (48.5)	45 (44.6)	0.001
	Low	7 (6.9)	0	
8th week	Normal	51 (50.5)	44 (43.6)	0.001
	Low	5 (5.0)	1 (1.0)	

*McNemar test

TSH - Thyroid - stimulating hormone, 4 week; serum TSH level in patients 4 weeks after receiving the contrast agent, 8 week; serum TSH levels in patients after 8 weeks of receiving the contrast to agent, TSH (µ / UlmL), range (0.55 - 4.7)

While 82.2% of patients detected by both measurements found to be normal, 2% of the patients found to have large thyroid volume and low TSH levels. Non-random compliance between the two measurements (Cohen Kappa=0.127) was found to be 42.3% (Table 5). There was a statistically significant negative relationship between thyroid volume and baseline TSH levels (r=-0.287; p=0.01); between thyroid volume and TSH levels at week 4 r=-0.341; p=0.001); between thyroid volume and TSH levels at week 8 (r=-0.332; p=0.001) (Fig.1).

Ultrasound examination of thyroid gland

In ultrasound examination of thyroid of 101 patients included in the study, nodules were seen in 55.4% (n=56) of the patients. A discrepancy was statistically observed between nodule and TSH level on 4th week (p <0.01). A discrepancy was statistically observed between nodule and TSH level on week 8 (p<0.01) (Table 6). In patients without thyroid nodules; median value of TSH levels were determined as following: on week 4-1.84 (25-75% percentile, 1.39 to 2.44) and on week 8-1.58 (1.18 to 2.40) and this change was found to be statistically reasonable.

Discussion

In our study, thyroid function test was normal before procedure of coronary angiography in all the patients included in the

current study. However, TSH level was low in 7 (6.9%) patients at week 4 and in 6 (5.9%)-at week 8. Significant decreases were observed in TSH levels at week 4 ($p<0.01$) and at week 8 ($p<0.01$) compared to baseline TSH levels. No statistically significant changes were found in serum free T3 and free T4 levels at weeks 4 and 8 compared to baseline fT3 and fT4 levels ($p>0.05$).

The iodine-containing contrast media for imaging purposes such as coronary angiography (CA), is widespread use result in considerable iodine load of the thyroid gland, which is mainly caused by in vivo deiodination of the contrast medium (17, 18). Several studies have reported thyroid dysfunction following administration of contrast agent (16, 19-22).

Sodium-iodide symporter and iodine into the thyroid follicular cells is active transport. Here, it participates into some reactions that cause the synthesis of thyroid hormones. As a result of organification, hormonally active iodothyronine, T4 and T3 precursor monoidotyrosines and diiodotyrosines occurs. When the intracellular concentration of iodine is high organification process is blocked temporarily. These autoregulatory mechanisms protect the thyroid from iodide excess while ensuring adequate iodide uptake for hormone synthesis (23, 24).

Iodine induced hyperthyroidism is a thyrotoxic condition caused by exposure to excessive iodine. It is also known as the Jod-Basedow phenomenon (25).

Jod Basedow is often detected in the areas with iodine deficiency and with patients with Hashimoto's thyroiditis, autoimmune thyroid disease, nodular thyroid disease (20, 26).

Today it is an accepted theory that in subjects with preexisting thyroid autonomy, iodine contamination can result in iodine-induced thyrotoxicosis. Iodine deficiency is an important factor for the development of autonomy and goiter and with the size of the goiter the probability of autonomy rises (27-29). It has been found in study of Roti et al. (26) that incidence of iodine-related hyperthyroidism reached to 1.7% in the regions of iodine deficiency while it remained much lower in the regions with adequate iodine. Advanced age, large thyroid volume, multinodular goiter and thyroid autonomy make the risk group in development of iodine-related thyrotoxicosis (27). The history of nontoxic diffuse or nodular goiter that occurs most frequently in the areas of iodine deficiency could not be well ascertained in Rhee et al. (22), although this is the most commonly reported risk factor for iodine-induced hyperthyroidism.

In a study by Conn et al. (30) thyroid function was studied following injection of non-ionic contrast agent in 73 subjects (of whom 51 had undergone coronary angiography and remaining subjects had undergone intravenous pyelogram (IVP), computed tomography (CT) and other angiographic procedures) aged between 50 and 84 years (mean age: 65.7 years). It was seen in that study that T4 level increased, TSH value decreased and no significant change occurred in T3 level. Two of these subjects developed hyperthyroidism and one subject was reported to develop atrial fibrillation (30). Rhee et al. (22) report the findings of a nested case-control study examining associations between exposure to iodinated radiologic contrast media and development of incident thyroid dysfunction. They describe significant associations between contrast exposure and the development of hyperthyroidism.

In a study by Martin et al. (11) development of hyperthyroidism following use of contrast agent for radiographic purposes was retrospectively investigated in patients between 70 and 96 years old (mean age: 80 years). It was found that contrast agent had been used previously in 7 (25%) of 28 subjects with hyperthyroidism undergoing investigation for this purpose. In 5 of these subjects, increase in level of fT4 and decrease in level of TSH was seen 3 to 6 weeks after the injection of contrast agent. Three of these subjects had clinically goiter whereas two were found to have big thyroid gland (11). In another study by Martin et al. (31), it was found that 23% of 60 patients above 70 years old had undergone a radiological investigation with a contrast agent in a period of 6 months before detection of their disease.

Patients' ages ranged between 20 and 85 years and the mean is 59.50±12.23 years. The median basal TSH level is in the range of 1.49 (25-75% percentile, 1.13 to 2.21) and within normal limits. In 4^{th} week, the TSH median level was 1.45 (25-75% percentile, 0.92 to 1.98) and 7 (6.9%) patients had TSH levels below the normal range (subclinical hyperthyroidism) ($p<0.01$) and in 8^{th} week, the TSH median level was 1.40 (25-75% percentile, 0.87 to 1.89) (5.9%) and 6 patients had TSH levels below the normal range (subclinical hyperthyroidism).

It was concluded in the present study that decrease in TSH level was more prominent in evaluating thyroid function. Elevation in serum T4 level may occur later. Moreover, it has been reported that some subjects might have hyperthyroidism despite normal T4 value. Thus, TSH values are advocated for being a more valuable indicator of thyroid function (4). In the present study, the fact that TSH level was found to be low in 7 patients at week 4 and in 6 patients at week 8 supports the view that TSH is a valuable parameter. Since elevation in serum level of fT4 might occur later, thyroid function was checked at weeks 4 and 8 in our subjects and no significant differences were found compared to the baseline fT4 and fT3 levels ($p>0.05$). In the present study, no serious clinical finding was found and pharmacological treatment was not necessary in the subjects in whom subclinical hyperthyroidism was found in follow-up at weeks 4 and 8 following injection of contrast agent. Our study shows that the patients with subclinical hyperthyroidism, that main symptoms of disease are fatigue, malaise, and was sweating. Patients with subclinical hyperthyroidism are closely being followed in our clinic.

Independent predictor of cardiac death is represented by subclinical hyperthyroidism (SCH) for the reason that the survival rate in SCH is lower than that in euthyroidism (32). A single measurement of low serum thyrotropin in individuals aged 60 years or older is related to the increase in mortality from all causes, and in particular mortality from all basis, and in particular mortality due to circulatory and cardiovascular disease (33).

Patients with underlying, perhaps mild, autoimmune thyroid disease, such as Hashimoto's thyroiditis, are particularly suscep-

tible to develop abnormal thyroid function over the ensuing several weeks after exposure (34, 35). It has been reported that iodine administration in these patients might cause hypothyroidism as well as more rarely might cause hyperthyroidism (36). In the present study, there were 4 (4%) anti-TPO positive patients while there were 2 (2%) antiTG positive patients. Reason for the fact that neither subclinical nor overt hypothyroidism was seen in the present study may be due to low rate of anti-TPO and antiTG positivity.

In the present study, mean thyroid volume was 15.14±7.67 mL in women with thyroid volume being large in 8 (26.7%) women while it was 16.28±6.51 mL in men with thyroid volume being large in 6 (8.5%) men. Thyroid volume showed significant relationship with TSH levels at 4 and 8 weeks (p>0,05). A negatively significant correlation was found between thyroid volume and TSH values at baseline and at weeks 4 and 8. These findings support the relationship between TSH suppression following administration of iodine-containing contrast agent and enlargement in thyroid volume in the regions of iodine deficiency.

Thyroid nodules are common clinical findings (35). Nodule was found in thyroid gland of more than half of the patients (55.4%) (n=56) undergoing thyroid ultrasound examination before coronary angiography. A discrepancy was statistically observed between nodule and TSH level on 4 week (p<0.01). A discrepancy was statistically observed between nodule and TSH level on week 8 (p<0.01).

In a study carried out by Fassbender et al.(37) on 102 patients that 16 had nodular thyroid gland, 15 had diffuse goiter and 34 had nodular goiter. It was observed that functional parameters changed related to thyroid morphology following coronary angiography even though the patients had no hyperthyroidism. It was noted in the study by Martin et al. that 4 out of 7 patients receiving radiocontrast agent before had multinodular goiter. It was stated out in another study carried out on an area of adequate iodine this might be caused by autonomy due to thyroid nodules (11).

Prevalence of subclinical hyperthyroidism is 1 to 2% in general population. In our study, the number of patients who are above 65 and over are 37 (%), and no reasonable change was determined on these patients serum TSH measurements (p<0.05); according to basal TSH, no reasoble change was detected on week 4 (p>0.05): the reduction observed in week 8 is reasonable (p<0.05). Progression to overt disease occurs at a rate of 1%-2% per year when TSH is <0.1 μIU/mL, and up to 5% per year in patients with multinodular goiter (13). Patients over age of 65, according to the TSH measurements, no reasonable change was determined (p<0.05); although no significant change was observed on week 4 compared to the baseline (p>0.05), there was a reasonable decrease compared to the baseline on week 8 (p<0.05).

Subclinical hyperthyroidism poses serious risk of morbidity and potential mortality in the elderly and especially in those with cardiac conditions (30). Cardiovascular effects of subclinical hyperthyroidism include an increase in average heart rate, increased risk of atrial arrhythmias, increased left ventricular mass, and reduced heart rate variability (38). Thus, it must be kept in the mind that subclinical hyperthyroidism may develop following injection of contrast agent especially in the elderly population (30, 39).

A mildly altered thyroid status is associated with an increased risk of mortality in patients with cardiac disease (32).

Study limitations

Prior to the administration of the iodine containing contrast agents in patients included in the study and 4 and 8 weeks after the administration of contrast agents, the main limitations of the study was the lack of measurement of the amount of free iodine excreted in the urine and was the lack of control group.

Future clinical implications

Investigating the effect of long-term mortality and morbidity of contrast agents, especially in areas with iodine deficiency, with higher number of patients with and without underlying thyroid disease, may result in beneficial clinical outcomes.

Conclusion

In conclusion, the use of iodine-containing radiological contrast agents may cause subclinical hyperthyroidism. This problem may be seen more frequently in the regions with a high incidence of iodine deficiency. Clinicians should be aware of this phenomenon and repeat TSH measurement in the case of an abnormal result at a later time point. It has to be emphasized that especially in areas of iodine deficiency, with more patients are needed in the study.

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