RESEARCH

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Evaluation and comparison of sonographic changes and thyroid function in iodinated intravenous contrast recipients and normal population

Leyla Halakouei[1], Ali Hekmatnia[1], Maryam Farghadani[1], Farzaneh Hekmatnia[2]✉

Purpose: **This study was aimed to Evaluation and Comparison of Sonographic Changes and Thyroid Function in Iodinated Intravenous Contrast Recipients and Normal Population in Isfahan.** ***Methods:*** **In a clinical trial study, 65 patients who exposed to Iodinated Intravenous Contrast and 92 patients who Recipients and non-exposed to Iodinated Intravenous Contrast were followed for 3 months after exposed to contrast. Thyroid function hormones, thyroid volume and thyroid nodule size were measured in the before intervention and 1 and 3 months after and compared between the two groups.** ***Results:*** **There was no significant difference between the two groups in terms of mean of thyroid volume before exposed (P=0.20) and three months after (P=0.96). The mean of nodule size was not significantly different between the two groups at any time (P> 0.05).** ***Conclusion:*** **In our patients we weren't found statistically different between exposed and non-exposed patients in changes of thyroid volume, nodule size and thyroid function but according to our limitation of the study, we offer evaluation of thyroid function tests before angiography.**

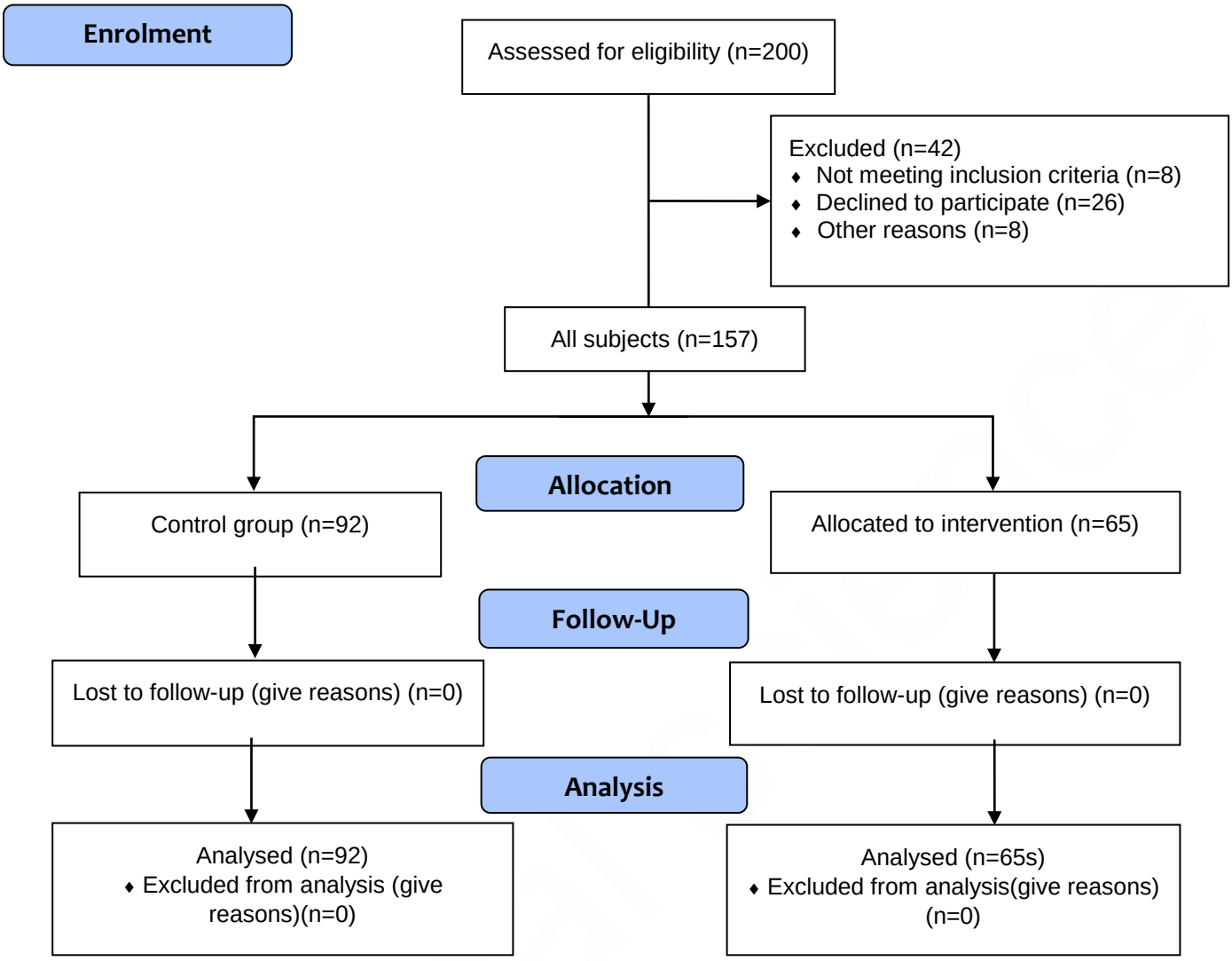
INTRODUCTION

Hyperthyroidism and hypothyroidism increase the risk of cardiovascular disease and can be associated with higher mortality rate (1, 15). Although the incidence of thyroid disturbances following exposure to iodinated contrast is low, this contrast is commonly used in diagnostic modalities and therefore, the emergence of these disorders is of particular importance (2). Guidelines have suggested that people with known hyperthyroidism should be evaluated for thyroid function after exposure to iodinated contrast (3). This proposal seems to be applicable to people with no previous history of thyroid disease, especially those who are frequently subjected to diagnostic modalities with these contrasts and who are over 40 years old (2). Some studies have shown that those who received iodinated contrast had a 1.17-fold higher risk of thyroid disorders and among these disorders; hypothyroidism was the more common (2). The reduced production of thyroid hormones is transient and improves after the adaptation of the body to these conditions. This adaptation and alignment with the reduction of the expression of sodium-iodine symporter is associated with follicular thyroid cells (4). Many studies have argued that after exposure to iodinated contrast, a hypothyroidism is to follow known as the Wolff-Chaikoff phenomenon. People susceptible to these disorders are specific age groups (embryos, infants and the elderly) and those with underlying thyroid disorders (5, 6). Although this hypothyroidism state is transient, and is recovered 2-3 weeks after iodine withdrawal, some patients will have permanent hypothyroidism and will need treatment subsequently (6). The conversion of transient hypothyroidism into a permanent state suggests that failure in escaping the Wolf-Chaikoff phenomenon might be related to autoimmune thyroid disorder or structural abnormalities of the thyroid gland (7). Routine screening for hypothyroidism is not done in patients after exposure to iodinated contrast. However, it is recommended to check the thyroid function after using these types of contrast in people with underlying thyroid disease. This study was carried out with the aim of comparing ultrasound findings and the thyroid gland function in iodinated intravenous contrast recipients against normal population in Isfahan. The rationale behind this aim is: 1) The increased use of modern diagnostic modalities and subsequently, increased use of iodinated contrast agents. 2) The controversy around the effects of this type of contrast on the incidence of hypo or hyperthyroidism, as well as the lack of a study that examined ultrasound changes after using these types of contrast.

MATERIAL & METHODS

This is a clinical trial study performed in Al-zahra hospital in Isfahan in 2016. The target population of the study were CT angiography patients with iodinated contrast media (100 cc) referred to the radiology department of Al-Zahra Hospital. The inclusion criteria for entering this study was age over 18 years old, candidate for CT angiography with

[1]Department of Radiology, Medical School, Isfahan University of Medical Sciences, Isfahan, Iran; [2]Department of Radiology, Alzahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran;
✉*Correspondence author:* Farzaneh Hekmatnia, Department of Radiology, Alzahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran. Email: farzanehhekmatniaradiology@gmail.com; Tel: +447403345007



Flowchart 1 CONSORT 2010 Flow Diagram

iodinated contrast agent, having no other drug that interferes with iodinated contrast media and satisfaction with participation in this study while having lack of sensitivity to the contrast media. On the other hand, the patient's refusal to participate in the study and cessation of CT angiography were considered as exclusion criteria.

The sample size required for the study was estimated to be 65 in each group using the sample size formula to compare the means, 95% confidence interval, 80% test power, thyroid volume standard deviation estimated as 1.7 (9), and the least significant difference between the two groups which was considered as 0.8.

Following permission from the Medical Ethics Committee of the University, 65 patients with CT angiography with iodinated contrast agent were selected and consented to participate in the study. They were examined by a radiologist, prior to CT angiography under the thyroid ultrasonography and their findings were recorded, also a blood sample was collected and sent to the Sedigheh Tahereh Research Center of Isfahan for thyroid function tests. After CT angiography, patients were re-examined on two further occasions, a month and three months later and on these days, they were again subjected to thyroid ultrasound and thyroid function tests. All ultrasounds were performed by an expert radiologist and thyroid function tests were performed by a laboratory and a device. In addition, 100 healthy individuals (1.5 times the size of the control group), matched on age and sex with the patient group, were selected from other participants in the hospital. Following informed consent, they underwent ultrasonography and thyroid function tests on the first day, one month and three months later. Thyroid ultrasonography was performed for all patients and controls by one radiologist and thyroid function tests were done by one laboratory. The method of calculating the thyroid volume was multiplying the length by the width of the gland at a thyroid thickness of 0.52. The echogenicity of the thyroid was divided into three groups according to the cervical strap muscles: hyperecho, isoecho and hypoecho. Additionally, the thyroid tissue heterogeneity and the presence or absence of nodules and their sizes in the thyroid was studied (22). All patient information was entered into SPSS software version 24 by two trained team members in order to reduce chances of data entry error. The data was statistically analysed by t-test, chi-square and ANOVA with repeated observations.

RESULTS

In this study, 65 patients underwent CT angiography with iodinated contrast agent and 100 healthy participants were enrolled as controls. During the study, 8 participants from the control group were excluded due to lack of referrals. Therefore, statistical analysis was performed on 65 patients and 92 controls. The implementation process of the intervention is shown in flowchart 1. The two groups did not differ significantly in term of age, gender and BMI distribution (Table 1).

Table 1 Frequency distribution of the sex of the patients in two groups

variables		Groups		P
		exposed	Non exposed	
Mean age(year)		60.1±10.3	59.8±14.02	0.81
sex	Male	38(58.5)	48(52.2)	0.69
	female	27(41.5)	44(47.8)	
Body Mass Index	Normal	16(24.6)	31(33.7)	0.69
	Over weight	41(63.1)	44(47.8)	
	Fat	8(12.3)	17(18.5)	

Table 2 Average volume of thyroid gland, nodule and parenchyma thyroid echogenicity in the two groups

variables	Time		Groups		P*
			exposed	Non exposed	
Thyroid volume(cc)	Before		5.9±1.4	5.6±1.4	0/20
	1 month after		6.2±1.03	5.7±1.4	0/005
	3 months after		5.63±1.3	5.64±1.4	0/96
	P**		<0.001	0.72	0.17***
Thyroid nodule size (mm^2)	Before		54.1±32.2	56.7±45.1	0.995
	1 month after		56.8±26.8	52.9±44.1	0.99
	3 months after		54.2±26.5	58.1±49.4	0.995
	P**		0.99	0.49	0.95
Thyroid gland echogenicity	Before	Heterogeneous	19(29.2)	25(27.5)	0.78
		Homogeneous	46(70.8)	67(72.8)	
	1 month after	Heterogeneous	21(32.3)	31(33.7)	0.86
		Homogeneous	44(67.7)	61(66.3)	
	3 months after	Heterogeneous	21(32.3)	27(29.7)	0.69
		Homogeneous	44(67.7)	65(70.7)	
	P**		0.51	0.03	*

*Mean difference at any time between the two groups based on t-test
**Trend of changes in each group based on ANOVA
*** Trend of changes between two groups based on ANOVA

Table 3 Mean and standard deviation of thyroid hormones in the two groups

variables	Time	Groups		P*
		exposed	Non exposed	
T3(nano.gr/d.Lit)	Before	1.6±0.6	1.7±0.3	0.50
	1 month after	1.8±0.5	1.8±0.3	0.55
	3 months after	1.9±2.3	1.2±1.8	0.70
	P**	0.03	0.007	0.7***
T4(nano.gr/d.Lit)	Before	9.1±2.3	8.8±1.6	0.28
	1 month after	9.2±2.2	8.6±1.5	0.035
	3 months after	8.7±1.9	8.8±6.2	0.93
	P**	0.02	0.62	0.47***
TSH(micro.gr/d.Lit)	Before	2.8±2.2	3.1±3	0.68
	1 month after	3±1.1	3.2±2.4	0.58
	3 months after	4.1±2.5	3.5±2.9	0.39
	P**	0.09	0.30	0.95***

*Mean difference at any time between the two groups based on t-test
**Trend of changes in each group based on ANOVA
*** Trend of changes between two groups based on ANOVA

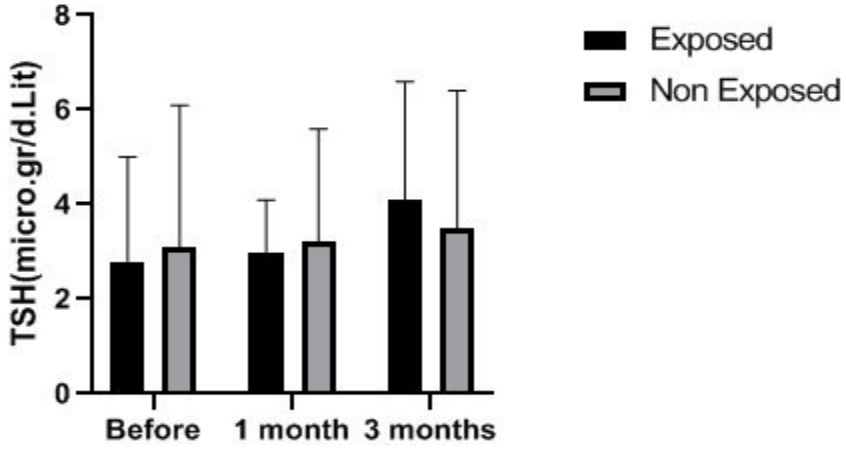


Figure 1 Thyroid function hormones (TSH) before and 1 and 3 months after intervention

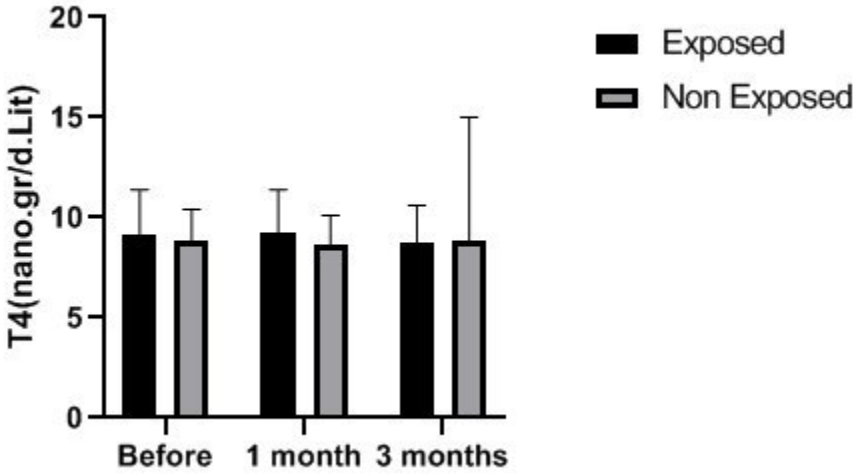


Figure 2 Thyroid function hormones (T4) before and 1 and 3 months after intervention

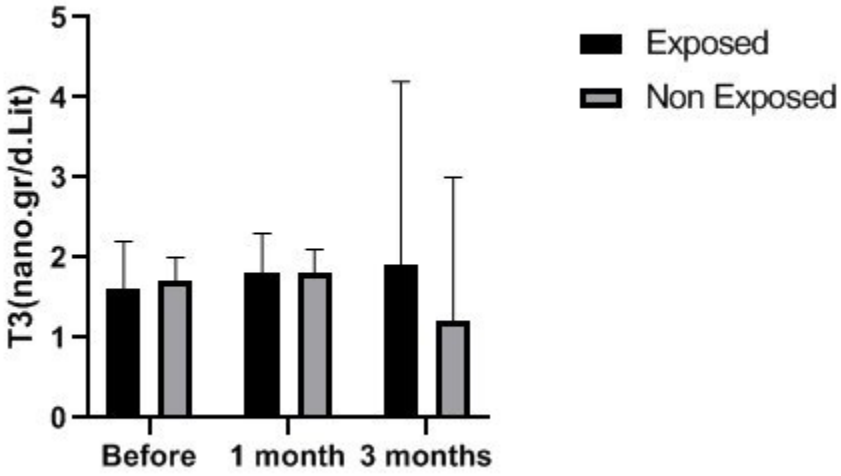


Figure 3 Thyroid function hormones (T3) before and 1 and 3 months after intervention

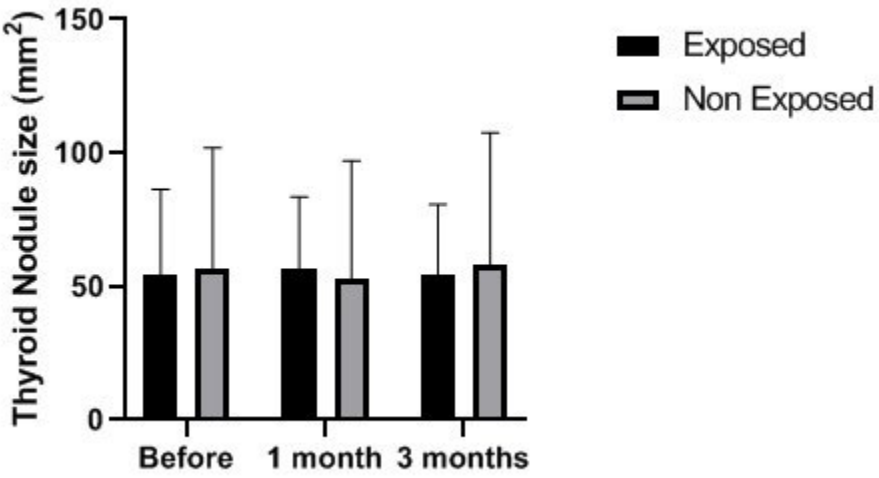


Figure 4 Thyroid Nodule Size before and 1 and 3 months after intervention

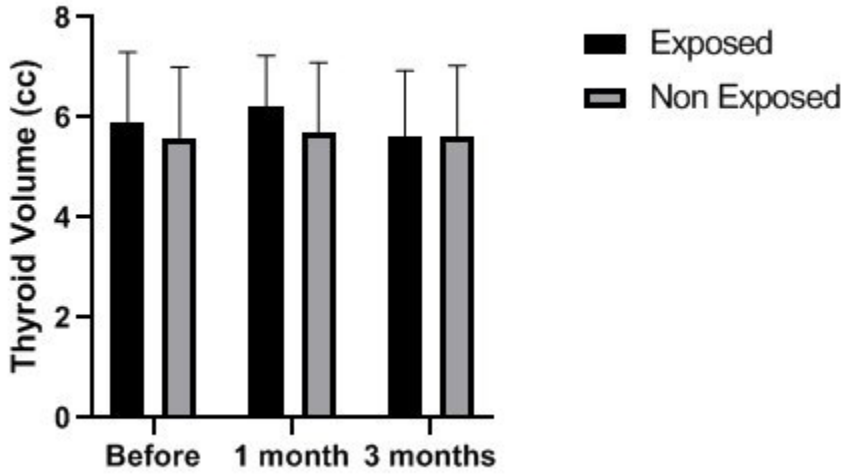


Figure 5 Thyroid Volume before and 1 and 3 months after intervention

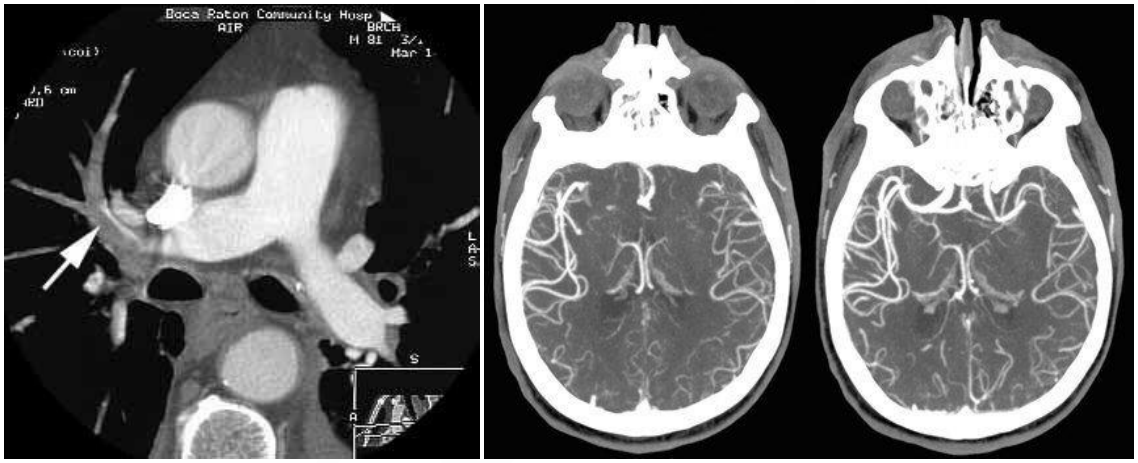


Figure 6 CT angiography with iodinated contrast agent

There was no significant difference between the two groups in terms of mean of thyroid volume before intervention (P = 0.20) and three months after intervention (P = 0.96). However, the mean was significantly higher in the intervention group than the control group (P = 0.005) one month after intervention in the test group. ANOVA test with repetition of observations showed that there was no significant difference in term of mean volume of thyroid gland in the control group during the three mentioned periods (P = 0.72). Conversely, there was a significant difference (P <0.001) in the test group. According to the mentioned test, changes in thyroid volume did not differ significantly between the two groups (P = 0.17).

Based on the results, the mean of nodule size was not significantly different between the two groups at any time (P> 0.05). ANOVA test with repeated observations showed that the mean of nodule size in the test group (P = 0.99) and control (P = 0.49) was not significantly different between the three times. According to the aforementioned, nodule volume changes during the intervention period between the two groups were not significantly different (P = 0.95). The analysis of parenchyma echogenicity showed no significant difference between the two groups in both periods. However, Cochran test showed that the frequency distribution of parenchyma in the test group was no significant difference between the three times (P = 0.51). There was a significant difference between the three groups in the control group (P = 0.03). Results are shown in Table 2.

Table 3 shows the mean and standard deviation of thyroid hormones levels at the time of the study. Based on independent t-test, mean T3 was not significantly different in any of the three times between two groups (P> 0.05). ANOVA test with repeated observations showed that T3 mean in test group (P = 0.03) and in control group (P = 0.007) was significantly different in three times, but the trend of T3 level changes between the two groups was not different (P = 0.7). There was no significant difference between the mean T4 before intervention (P = 0.28) and three months after the intervention (P = 0.93), but in the experimental group one month after the intervention T4 was significantly higher than the control group (p=0.035). ANOVA test with repeated observations also showed that the mean of T4 in the control group was not significantly different between the three times (P = 0.62), but in the test group, there was a significant difference between the three times (P = 0.02). However, based on the test, the trend of T4 changes was not different between two groups (P = 0.47). The evaluation of TSH levels during these periods did not show any significant difference at any time between the two groups. Additionally, ANOVA test with repeated observations showed that the mean of TSH in the test group (P = 0.09) and control (P = 0.30) was not significantly different between

the three times and the trend of TSH level changes were not different in the two groups (P = 0.95).

DISCUSSION

The incidence of thyroid disorders in patients undergoing CT angiography with iodinated contrast agents has become a controversial topic amongst radiologists, endocrinologists. Although thyroid disorders are transient in these patients, cases of permanent dysfunction have been observed. But these changes have not yet been addressed from an ultrasound perspective. Therefore, the present study was conducted to compare ultrasound and thyroid gland function in intravenous iodine and normal population recipients in Isfahan. In this study, the thyroid morphology and its functional hormones were compared and evaluated pre-interventional, one month and three months later in two groups of patients (which were subjected to CT angiography with iodinated contrast agent) with 92 controls (which were not exposed to the mentioned contrast agent). There were no significant differences between the two groups in terms of age, sex distribution and body mass index, and there was no conclusive effect on the factors. Therefore, the observed differences between the two groups are likely to be related to the type of contrast agent.

Compared to the results of our study, thyroid volume in the test group increased significantly in one month after receiving the iodinated contrast agent, but after three months, the thyroid gland volume was similar between the two groups as before. In other words, iodinated contrast agent injection has been shown to increase transient volume in the thyroid gland. Thyroid nodules and also thyroid gland parenchyma showed that exposure to iodine-containing contrast does not have a significant effect on the volume of the nodule or the parenchymal state of the thyroid gland. In a study by Rhee et al., exposures to iodinated contrast have been associated with the progression of hypothyroidism in subjects without underlying thyroid disease (8). Studies of rare cases of hyperthyroidism have been reported in patients without underlying thyroid disease following elevated iodine intake (9, 10). Studies have shown that thyroid dysfunction may increase after administration of iodinated contrast, even in cases where the patient has no thyroid abnormalities. Therefore, when hyperthyroidism is detected by iodine contrast, iodine exposure should be avoided further. Patients should be examined in terms of thyroid function after multiple exposures with iodinated contrast. Although hyperthyroidism is transient in the presence of iodine, it is improved after withdrawal. Symptomatic patients should be treated with beta blocker or methimazole, and in high-risk cases, it should be prescribed on a doctor's decision.

Evaluation of the level of functional hormones in the thyroid showed that exposure to iodinated contrast has no significant effect on the level of thyroid hormones and although T3 and T4 level changes were significant before exposure, until the 3 months after exposure, there was no significant difference between the two groups in the changes in the levels of the hormones between the two test groups and control. However, according to the Gartner et al., exposure to these substances in participants with no underlying thyroid disease increased the level of TSH that occurred within 3-5 days after exposure but the level of T3 and T4 did not change (11). In a study by Breuel et al., which was conducted on 39 patients exposed to iodine contrast, the contrast increased T3 levels and decreased TSH levels (12). Another cohort study by Conn et al. on 73 patients with an average age of 65.77 years showed that after exposure to iodinated contrast agents, hypothyroidism occurs in patients (13). A further case-control study by Rhee et al. showed people without thyroid disease, getting an iodinated contrast dose can increase the thyroid dysfunction by 2-3 times (14). The same researcher has shown in another study that there is a meaningful relationship between exposure to iodine and hypothyroidism (8).

CONCLUSION

Results of the current study indicate that although significant changes could occur in patients receiving iodine contrast regarding the size of thyroid, its nodules or hormones, no significant difference could be observed between these patients and those who are not exposed to iodine contrast. Thus, considering the results of previous studies time on the potential negative effects of these contrasts on thyroid function and the potential neglect of post contrast pathological changes due to unobserved at a specific points, routine post iodine contrast assessments on patients receiving contrast could be considered as a beneficial screening method in order to diagnose, prevent or treat contrast induced thyroid abnormalities. However, further studies in larger populations are necessary to confirm these findings and prepare adequate clinical guidelines in this regard.

Study limitations

This is a clinical trial study on a small number of patients under Ct-angiography which may lead to imprecise estimation of sonography findings. Furthermore, lack of comparison group pushed us just to describe findings.

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Ethical approval
The Ethics committee of the Isfahan University of Medical Sciences approved this study. Ethic code: IR.MUI.REC.1396.3.544.

Conflicts of interest
There are no conflicts of interest.

Author's Contribution
AH: Study idea, study design, interpretation and contribution in writing the paper
LH: contributed in data collection and data analysis and preparation of paper
MF: contributed in interpretation data and writing the paper
MF: contributed in interpretation of sonographic graphs
FH: contributed in data analysis

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