Thyroid Dysfunctions in Patients with Hepatocellular Carcinoma Treated by Transarterial Chemoembolization

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Background and study aim: Transarterial chemoembolization (TACE) techniques typically involve inserting a catheter into the hepatic segmental arteries that provide blood to hepatocellular carcinoma (HCC) lesions. The aim of the study was to evaluate the incidence and type of thyroid dysfunction in individuals diagnosed with HCC after TACE.

Patients and Methods: A cohort of 30 HCC cases deemed suitable for TACE was enrolled in this prospective study. Exclusion criteria included prior antiviral therapy, pre-existing thyroid conditions, or residency in regions with known iodine deficiency. Following informed consent, participants underwent comprehensive baseline evaluations including medical history review, physical exams, and laboratory evaluations: thyroid hormones (TSH, FT3, and FT4), renal and liver profile testing, these parameters were re-evaluated one week and one-month post-TACE.

Results: One week following TACE, elevated levels of TSH, FT3, and FT4 were observed in 4(13.3%), 2(6.7%), and 5(16.7%) patients, respectively, while reduced levels were noted in 1(3.3%), 2(6.7%), and 3(10%) patients, respectively. Normal levels were maintained in 25(83.3%), 26(86.7%), and 22(73.3%) patients, respectively, with statistically significant differences ($P< 0.05$). At the one-month follow-up, no patients exhibited elevated TSH, while 4(13.3%) and 9(30%) showed elevated FT3 and FT4, respectively. Low levels were recorded in 3(10%), 1(3.3%), and 0(0%) patients, respectively, with normal levels observed in 27(90%), 25(83.3%), and 21(70%) patients, respectively, again demonstrating significant differences ($p < 0.05$).

Conclusion: Thyroid dysfunction, manifesting as either hypothyroidism or hyperthyroidism, occurred in 16.7% of patients post-TACE, indicating a notable risk associated with this procedure.

INTRODUCTION

Transarterial chemoembolization (TACE) emerged as a palliative therapeutic option for unresectable hepatocellular carcinoma (HCC) cases and has since established itself as one of the predominant modalities within interventional oncology [1]. Contemporary TACE techniques typically involve inserting a catheter into the hepatic segmental arteries that provide blood to HCC lesions. This targeted approach seeks to maximize the therapeutic effect on the tumor while minimizing damage to the adjacent non-neoplastic hepatic tissue. The treatment combines a chemotherapeutic drug with iodide—in the form of iodized oil—such as lipiodol, which is used as a radiopaque contrast medium (CM), to improve its effectiveness [2].

Through the process of incorporating iodine into the double bonds of unsaturated fatty acids derived from specific plant oils, particularly poppy seed oil, which contains a high proportion of unsaturated fatty acids, [3]. As an iodinated contrast medium (ICM), lipiodol introduces a substantial iodine burden to the patient. A single dose provides roughly 13,500 micrograms of free iodide, along with 15 to 60 grams of bound iodine, which could later be converted into free iodide following administration [4, 5].

This amount of iodide surpasses the advised daily intake for adults of 150 micrograms by a factor ranging from 90 times to several hundred thousand times [6, 7]. Given this significant iodine exposure, the current work was intended to assess the incidence and characteristics of thyroid dysfunction in patients with HCC undergoing TACE.

PATIENTS AND METHODS

Study Design:

This cross-sectional study was conducted at the HCC Clinic in the Tropical Medicine Department of Ain Shams University Hospitals from June 2014 to December 2014.

The study enrolled 30 patients with confirmed HCC diagnoses according to the Barcelona Clinic Liver Cancer 2010 criteria, all providing written informed consent before undergoing TACE procedures [8]. Exclusion criteria were established to minimize confounding factors. They included patients with a history of thyroid disorders, those who had received antiviral treatment, and individuals residing in iodine-deficient geographical areas.eg upper Egypt governorates like Suhag, Qena, Luxor and Aswan. Rural and desert communities (New Valley and North Sinai).

Pre-TACE Clinical Assessment and Laboratory Investigations:

Before the TACE procedure, all patients underwent comprehensive clinical evaluations. A thorough medical history was obtained, and detailed physical examinations were performed, with particular attention devoted to manifestations of thyroid dysfunction. Laboratory investigations included CBC analysis, liver profile tests ALT and AST, renal function assessment (serum creatinine), and tumor marker evaluation (serum alpha-fetoprotein). Additionally, baseline thyroid function was assessed by measuring TSH, free T3, and free T4 levels.

Post-TACE Monitoring and Follow-up:

Following the TACE procedure, patients were systematically monitored for changes in thyroid function. The thyroid profile (TSH, free T3, and free T4) was re-evaluated at two distinct time points: one week and one-month post-procedure. Patients were re-examined clinically and questioned concurrently with laboratory tests about the development of manifestations indicative of thyroid dysfunction after TACE management.

Laboratory Methodology for Thyroid Function Assessment:

Thyroid function parameters were measured using B7K Architect free T3, free T4, and TSH reagent kits (U.S.A). The assay methodology employed was chemiluminescent microparticle immunoassay (CMIA), which enables quantitative determination of free T3, free T4, and TSH in human serum or plasma specimens.

Blood specimens were collected using standard venipuncture techniques in serum separator tubes or EDTA anticoagulant tubes for plasma. To ensure optimal assay performance, specimens were processed free of bubbles, fibrin, red blood cells, and other particulate matter. Full clot development in serum samples was confirmed before the centrifugation process began. For tests postponed beyond 24 hours, serum or plasma was isolated from the cellular elements. Specimens were stored at 2-8°C for up to 6 days; for longer storage periods, specimens were frozen at -10°C or below, which preserved assay performance characteristics.

Assay Calibration and Reference Ranges :

The free T3 assay utilized a calibrator range of 0.0-30.0 pg/ml, with results generated using a 4-parameter logistic curve fit data reduction approach (4PLC, Y-weighted). The default result unit was pg/ml; the formula concentration in pg/ml × 1.536 yields an alternative unit conversion to pmol/L. The accepted normal reference range was 1. 71–3. 71 pg/ml.

For free T4 assessment, the calibrator range was 0.0-6.0 ng/dl, also utilizing a 4PLC, Y-weighted data reduction method. The default result unit was ng/dl, with conversion to pmol/L available using the formula: concentration in ng/dl × 12.87 = concentration in pmol/L. The normal reference range was defined as 0.70-1.48 ng/dl.

The TSH assay employed a calibrator range of 0.0000-100.0000 µIU/ml, with the same 4PLC, Y-weighted calibration curve. The default unit was µIU/ml, with direct 1:1 conversion to

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mIU/ml available. The established normal reference range for TSH was 0.35-4.94 µIU/ml.

TACE Procedure Methodology:

The TACE procedure was performed using percutaneous endovascular techniques. Either 5-F catheters (Simmons 1 and Cobra; Mallinckrodt, St. José, USA or Hydrophilic Simmons 1 and Cobra; Terumo, Tokyo, Japan) or 3-F coaxial microcatheters (Tracker 18; Vascular Access System, Target, St. José, USA; SP Catcher; Terumo) selective catheterization of the hepatic segmental arteries supplying the lesions.

The TACE approach facilitated direct delivery of potent anticancer agents to tumor-feeding arteries, resulting in high intratumoral drug concentrations while minimizing systemic exposure. To guarantee uniform emulsion, 100 mg adriablastin powder was painstakingly made by mixing 10 cc salty, water-soluble CM and 10 cc oily CM (lipiodol ultra-fluid). Gelfoam particles—cut into tiny pledgets and suspended in water-soluble CM before treatment—were used during the embolization phase.

Sample Size Calculation:

Using PASS 15 program for sample size calculation, setting confidence level at 90% and margin of error at 12.5%, it is estimated that sample size of 30 patients were enough to detect an expected incidence rate of thyroid dysfunction of 20%.

Statistical Analysis:

Data was analyzed using IBM SPSS Statistics (Version 22.0, IBM Corp., USA, 2013). Quantitative parametric measures were expressed as mean ± standard deviation, while quantitative non-parametric measures were presented as median and percentiles. Categorical data were expressed as both numbers and percentages. Statistical evaluations were performed using Ranked Spearman correlation and Chi-square tests. Statistical significance was defined as a probability of error at 0.05, with values at 0.01 and 0.001 considered highly significant.

RESULTS

Demographic and clinical characteristics of the study participants are shown in table 1 Subclinical alterations in thyroid hormone concentrations were observed in a subset of patients following TACE, with levels demonstrating either an increase or decrease relative to baseline. Regarding TSH levels, one-week post-TACE, elevated concentrations were recorded in 4 patients (13.3%), reduced levels in 1 patient (3.3%), and normal levels maintained in 25 patients (83.3%). By the one-month follow-up, TSH levels in the 4 patients with previously elevated values had normalized, while the single patient with a low TSH level persisted in this state. Additionally, among patients with normal TSH levels at one week, 2 (8%) exhibited reduced levels at one month, with these changes achieving statistical significance ($p < 0.05$) (Table 2).

With respect to FT4 levels, one week after TACE, 5 patients (16.7%) displayed elevated concentrations, and 3 patients (10%) showed reduced levels. At the one-month assessment, the number of patients with elevated FT4 increased to 9 (30%), while the 3 patients with initially low levels had normalized, with these shifts demonstrating statistical significance ($p < 0.05$) (Table 3).

Similarly, FT3 levels exhibited changes: one-week post-TACE, 2 patients (6.7%) had elevated FT3 levels, and 2 patients (6.7%) had reduced levels. By one month, 4 patients (13.3%) presented with elevated FT3 levels, and 1 patient (3.3%) exhibited a reduced level but these shifts are not statistically significant (Table 4).

Furthermore, there were no notable correlations between the observed alterations in thyroid hormone levels and variables such as age, sex, residence, or baseline laboratory parameters ($p > 0.05$). These findings suggest that while TACE induces detectable changes in thyroid function, these variations are not consistently associated with demographic or clinical covariates in this cohort.

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Table 1: Demographic data of the studied group.

Variables		**Mean ± SD**	**Range**
Age (years)		54.9±5.17	(43-64)
Variables		**Number**	**Percent %**
Gender	**Male**	24	80%
	Female	6	20%
Smoking	**Smoking**	7	23%
	Non-Smoking	23	77%
Residence	**Urban**	6	20%
	Rural	24	80%
Dm	**Diabetic**	12	40%
	Non-Diabetic	18	60%
Child Class	**A**	18	60%
	B	12	40%

Data is presented as Mean ± SD& percentage.

Tables 2: Changes in TSH levels.

			1m	**1w**	**Bef.**	**Total**
TSH	**High**	**Count**	0	4	0	4
		%	0.0%	13.3%	0.0%	4.4%
	Low	**Count**	3	1	0	4
		%	10.0%	3.3%	0.0%	4.4%
	Normal	**Count**	27	25	30	82
		%	90.0%	83.3%	100.0%	91.1%
Total		**Count**	30	30	30	90
		%	100.0%	100.0%	100.0%	100.0%
		Value		**P**		
Pearson Chi-Square		11.963[a]		0.018		

Data is presented as percentage (%). TSH: Thyroid-Stimulating Hormone.

Tables 3: Changes in FT4 levels.

			1m	**1w**	**Bef**	**Total**
FT4	**High**	**Count**	9	5	0	14
		%	30.0%	16.7%	0.0%	15.6%
	Low	**Count**	0	3	0	3
		%	0.0%	10.0%	0.0%	3.3%
	Normal	**Count**	21	22	30	73
		%	70.0%	73.3%	100.0%	81.1%
Total		**Count**	30	30	30	90
		%	100.0%	100.0%	100.0%	100.0%
		Value		**P**		
Pearson Chi-Square		**16.714[a]**		**0.002**		

Data is presented as percentage (%). FT4: Free Thyroxine

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Tables 4: Changes in FT3 levels.

			1m	1w	Bef	Total
FT3	High	Count	4	2	0	6
		%	13.3%	6.7%	0.0%	6.7%
	Low	Count	1	2	1	4
		%	3.3%	6.7%	3.3%	4.4%
	Normal	Count	25	26	29	80
		%	83.3%	86.7%	96.7%	88.9%
Total		Count	30	30	30	90
		%	100.0%	100.0%	100.0%	100.0%
		Value		P		
Pearson Chi-Square		4.825[a]		0.306		

Data is presented as percentage (%)

DISCUSSION

Excessive iodide accumulation within the thyroid can paradoxically inhibit iodide organification and subsequent thyroid hormone synthesis, a phenomenon initially characterized in vivo in rats by Wolff and Chaikoff in 1948, known as the "acute Wolff-Chaikoff effect" [9, 10]. Although iodide excess initially suppresses thyroid hormone synthesis, this effect is usually transient, and hormone production resumes despite continued iodine exposure. Thought to be "adaptation" or "escape" from the acute Wolff-Chaikoff effect, this adaptive response shields the thyroid from iodine-induced hypothyroidism and goiter formation [11].

This study aimed to evaluate thyroid gland malfunction in HCC patients after TACE. Our results showed subclinical variations in thyroid hormone levels after TACE, which presented either increases or decreases. Post-TACE, TSH was transiently elevated (13.3%, normalizing by one month) or reduced (3.3%, persistent); 8% of initially normal cases developed low TSH (*p* < 0.05). FT4 elevations increased from 16.7% to 30% by one month, with normalization of initially low levels (*p* < 0.05). FT3 fluctuations (6.7–13.3%) were non-significant (*p* > 0.05). No clinical thyroid dysfunction occurred

Previous research provides context for these observations. A controlled study reported ICM exposure linked to thyrotoxicosis, recording 76 occurrences of incident overt hyperthyroidism and 178 cases of incident hypothyroidism in an area adequate in iodine [12]. Retroactively looking at thyroid dysfunction after TACE in 219 individuals with histologically confirmed HCC treated between 1997 and 2007 Flohr et al. [13]. Of the 138 individuals with known TSH data, 19 had subclinical hyperthyroidism, and 23 (16.7%) post-TACE developed clinical hyperthyroidism needing therapy. Conversely, TSH increased in 19 patients (13.8%), from a mean of 3.08 U/mL pre-TACE to 22.45 U/mL post-TACE (range: 4.59–76.66 U/mL), with 6 experiencing transient hypothyroidism that resolved within 3.2 months, while six others developed clinical hypothyroidism necessitating therapy [13].

There were 3,822 instances of hyperthyroidism, 7,001 cases of hypothyroidism, and 339,046 euthyroid controls found in separate case-control research within a community-based cohort with 349,869 patient intervals. Experiencing incident hyperthyroidism [odds ratio (OR) 1.61, 95% CI 1.27-2.04], overt hyperthyroidism [OR 1.62, 95% CI 1.08-2.43], and overt hypothyroidism [OR 2.01, 95% CI 1.25-3.23] were all increased risks linked with ICM exposure. The study included adults (≥18 years) with at least one normal (TSH) test between 1996-2012 and no prior thyroid disease, medications, or abnormal lab results, requiring a follow-up TSH test within 2 weeks to 2 years. Researchers identified cases of hyperthyroidism (low TSH) and hypothyroidism (high TSH), matched them with controls (normal TSH) by age, sex, and other factors, then analyzed associations with iodinated contrast media exposure using medical records and regression models. They found increased risks for both hyperthyroidism and severe hypothyroidism [14].Additional support for these conclusions comes from smaller studies: 4 out of 22 German patients [15] And 3 out of 56 US patients [16] developed subclinical

hypothyroidism one week after coronary angiography or iodinated CT. A Japanese study of 214 women found that women with pre-existing subclinical hypothyroidism were more likely to experience overt hypothyroidism post-hysterosalpingography (35% vs. 2% in euthyroid individuals) [17]. In individuals with nodular thyroid disease, in particular, iodine exposure has been linked to hyperthyroidism. An iodine-induced thyroid storm was recorded in a case report involving a 62-year-old Japanese lady 5 hours after CT with contrast [18]. Increased rates of hyper- and hypothyroidism, with a median start around 9 months post-exposure, were associated with the use of ICMs in a major U.S. case-control study that lasted 20 years in an iodine-sufficient area [12].

Regarding thyroid dysfunction in patients with HCC treated by TACE, the current study's limitations include the relatively small sample size (n=30) in this study reflects the strict inclusion and exclusion criteria applied to ensure homogeneity and minimize confounding variables. Participants were selected over a limited recruitment period, and eligibility required the absence of pre-existing thyroid disorders, prior antiviral therapy, and residence in iodine-deficient areas. These stringent criteria, while reducing potential bias, inevitably restricted the number of eligible patients. Nevertheless, the study provides valuable preliminary data on the impact of TACE on thyroid function in HCC patients, highlighting the need for further multicenter studies with larger cohorts and extended follow-up. Given the paucity of prior research on this subject, further studies are needed to build strong evidence base and guide clinical practice. This study was designed as a pilot study to explore the feasibility and potential associations, which justifies the limited number of participants.

CONCLUSION

Thyroid dysfunction occurred in 16.7% of patients post-TACE, indicating a notable risk associated with this procedure.

Acknowledgments :

Nil

Ethical considerations: The department's local ethical committee approved the investigation protocol, ensuring compliance with the 1975 Helsinki Declaration guidelines.

Data Materials and/or Code availability:

Data is available upon reasonable request from corresponding author.

Authors' contribution:

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by [A.T.A.], [A.A.E.] and [A. M. M.]. The first draft of the manuscript was written by [A. K. E.] and [D. M. G.] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript .

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Conflict of interest

The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.

HIGHLIGHTS

- Transarterial chemoembolization (TACE) emerged as a palliative therapeutic option for unresectable hepatocellular carcinoma (HCC) cases and has since established itself as one of the predominant modalities within interventional oncology.
- Contemporary TACE techniques targeted approach seeks to maximize the therapeutic effect on the tumor while minimizing damage to the adjacent non-neoplastic hepatic tissue. The treatment combines a chemotherapeutic drug with iodide—in the form of iodized oil—such as lipiodol, which is used as a radiopaque contrast medium (CM), to improve its effectiveness
- Thyroid dysfunction, manifesting as either hypothyroidism or hyperthyroidism, occurred in 16.7% of patients post-TACE, indicating a notable risk associated with this procedure.

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