International Journal of General Medicine

Dovepress

open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Impact of Hypothyroidism on Patients with Hepatocellular Carcinoma Undergoing Liver Transplantation

Ahmed Salman,[1] Mohamed Aon,[1] Amr Hussein,[2] Mohamed Salman,[3] Mohamed Tourky,[4] Ahmed Mahmoud,[5] Feras Aljarad,[6] Mohamed Elkaseer,[7] Hossam El-Din Shaaban,[8] Ahmed Moustafa,[9] Ahmed El-Mikkawy,[10] Nahla Gaballa,[11] Heba Abdallah,[12] Zaky Ftouh Zaky Rashed,[13,14] Hesham Elkassar[1]

[1]Internal Medicine Department, Faculty of Medicine, Cairo University, Cairo, Egypt; [2]Internal Medicine Department, Faculty of Medicine, Al-Azhar University, Cairo, Egypt; [3]General Surgery Department, Faculty of Medicine, Cairo University, Cairo, Egypt; [4]Department of Surgery, Great Western Hospitals NHS Foundation Trust, Swindon, UK; [5]Senior Clinical Fellow, Great Western Hospital NHS Foundation Trust, Swindon, UK; [6]Lewisham and Greenwich NHS Trust, Lewisham, London, UK; [7]General Surgery Department, Faculty of Medicine, Al-Azhar University, Cairo, Egypt; [8]Hepatology and Gastroenterology Department, National Hepatology and Tropical Medicine Research Institute, Cairo, Egypt; [9]Department of Endemic Medicine and Hepatology, Faculty of Medicine, Cairo University, Cairo, Egypt; [10]Hepatology and Gastroenterology Department, Theodor Bilharz Research Institute, Cairo, Egypt; [11]Anesthesiology and Intensive Care Department, National Liver Institute, Menoufia University, Shibin El Kom, Egypt; [12]Clinical Pathology Department, National Liver Institute, Menoufia University, Shibin El Kom, Egypt; [13]Anesthesiology and Intensive Care Department, Faculty of Medicine, Al-Azhar University, Cairo, Egypt; [14]Department of Anesthesia, College of Applied Sciences, Almaarefa university, Ad Diriyah, Riyadh, Saudi Arabia

Correspondence: Ahmed Salman
Internal Medicine Department, Faculty of Medicine, Cairo University, Egypt
Tel +20 1000468664
Email awea844@gmail.com

Background: This work endeavored to explore the effect of hypothyroidism on mortality in subjects with HCC who underwent living-donor liver transplantation (LDLT).

Methods: This prospective study included 107 patients with HCC subjected to LDLT, divided into hypothyroid group (n=53) and euthyroid group (n=54). The primary objectives were overall and disease-free survival (DFS).

Results: Euthyroid and hypothyroid groups were comparable in all baseline characteristics except the age of patients. Overall survival (OS) of the whole group at 48 months was 68.8%, while the DFS was 60.2%. On univariate analysis, OS was negatively affected by the older age of the patients ($p<0.001$) or the donor ($p<0.001$), hypothyroidism ($p=0.008$), HBV ($p=0.029$), larger tumor size ($p=0.023$), and defective Milan criteria ($p=0.022$). On multivariate analysis, the age of the patients and donors was the independent factor affecting OS. On univariate analysis, DFS was negatively affected by older age of the patients ($p < 0.001$) or the donor ($p=0.005$), hypothyroidism ($p=0.005$), HBV ($p=0.019$), larger tumor size ($p=0.023$), and defective Milan criteria ($p=0.020$). On multivariate analysis, the age of the patients, thyroid status, and Milan criteria were the independent factors affecting DFS.

Conclusion: Hypothyroidism is a risk factor for worse outcomes in HCC patients after liver transplantation.

Keywords: hypothyroidism, hepatocellular carcinoma, liver transplantation

Introduction

Globally, hepatocellular carcinoma (HCC) is the most frequent primary liver cancer representing the sixth most common malignancy.[1] In Egypt, HCC is the fourth common cancer.[2] The age-standardized incidence rate of HCC is 61.8 per 100,000 population.[3] The pathogenesis of HCC is a complex process linked to different predisposing factors. Liver cirrhosis is a chief risk factor for HCC development irrespective of its cause. Meanwhile, chronic viral infections, hepatitis B virus (HBV), and hepatitis C virus (HCV) are substantial risk factors for HCC.[4] Metabolic[5] and hormonal factors[6] were suggested to be implicated in the development of HCC.

Growing evidence indicated the involvement of thyroid hormones in the development of malignancies of the breast,[7] ovary,[8] and HCC.[9] Thyroid hormones (TH) are involved in regulating several physiological processes, such as cell development, structure, growth, and metabolism.[10] Thyroid disorders are commonly linked to many chronic comorbidities like diabetes mellitus,[11] chronic kidney disease,[12]

Received: 29 June 2021
Accepted: 31 August 2021
Published: 16 September 2021

and liver disorders.[13] Epidemiological data supposed a positive correlation between hypothyroidism and high risk of NAFLD and HCC.[14–16] Besides, experimental studies found that treatment with T3 can prevent liver diseases, including HCC in rodents exposed to carcinogens.[17,18]

These findings back a possible role TH in the progression and survival in patients with HCC. Therefore, the current work endeavored to explore the effect of hypothyroidism on mortality in patients with HCC undergoing liver transplantation.

Patients and Methods

This prospective multicentre cohort analysis involved 107 cases aged 18 years or more with HCC who underwent living-donor liver transplantation. The patients were divided into two groups according to the thyroid status: hypothyroid group (n=53) and euthyroid group (n=54). Patients were excluded if diagnosed with cholangiocarcinoma (CCA), mixed HCC, and CCA or fibrolamellar HCC based on explant pathology. Also, patients who developed hypothyroidism due to treatment of hyperthyroidism were not enrolled in the analysis.

The work was approved by the relevant ethical committee of Cairo and Al-Azhar University Hospitals and the National Liver Institute. All living-donor transplants were donated voluntarily with written informed consent, and that this was conducted in accordance with the Declaration of Istanbul. Also, this study was conducted in accordance with the Declaration of Helsinki.

The confirmation of HCC was based on either noninvasive parameters (a new lesion >1 cm in size evolving in a cirrhotic patient and depicted by arterial hyperenhancement and portal venous washout on computed tomography, magnetic resonance imaging, or angiography) or histopathology from the biopsy or the explanted liver, adopting the criteria of the American Association for the Study of Liver Disease (AASLD) 2010 Guidelines for HCC.[19] All cases were followed up for a median of 43 months (range: 1–58).

Data Collection

Demographic data, medical background, smoking history, laboratory workup, original liver disorders (including symptoms that indicate decompensation such as repeated spontaneous bacterial peritonitis (SBP), repeated hepatic coma, refractory fluid retention, and recurrent variceal bleeding), and HCC features from the explanted liver were registered. Medical history before the diagnosis of HCC, such as uncontrolled blood sugar, elevated blood pressure, hyperlipidemia, and hypothyroidism, were collected.

Pretransplant hypothyroidism was determined as a thyroid-stimulating hormone (TSH) level continuously over the year preceding transplant >5 mIU/L, a previously confirmed endocrinologist diagnosis, or the usage of thyroid hormone replacement medications.[20]

Original hepatic diseases were confirmed by positive HBsAg for HBV, positive HCV RNA or anti-HCV for HCV, previous undue alcohol consumption for alcoholic liver disease (ALD), metabolic syndrome associated with fatty infiltration for non-alcoholic fatty liver disease (NAFLD), and immunological and/or histopathologic confirmation for autoimmune liver diseases (AILD) including autoimmune hepatitis, primary biliary cholangitis, primary sclerosis cholangitis, and others. Cases were followed up for five years from the time of liver transplantation or till death.

The primary outcomes were overall and disease-free survival and recurrence rate. Overall survival was calculated from the time of operation to the time of death or last follow-up visit. Disease-free survival was calculated from the time of operation to the time of recurrence, death, or last follow-up.

Anesthetic Management

During the transplantation procedure, all patients were anesthetized by IV propofol (2mg/kg), Fentanyl (2mic/kg), and rocuronium (0.9 mg/kg) as a neuromuscular blocker, and blouses were given according to neuromuscular monitor and maintained by inhaled sevoflurane.

Lungs will be controlled by pressure-regulated volume-controlled mode, with a mixture of (Fio2 0.4) in air, and PEEP was applied after recruitment, PaCo2 was adjusted around 35 mmHg.

Rotational thromboelastometry (ROTEM) was used to guide transfusion of platelets, fresh frozen plasma, and cryoprecipitate perioperatively.

Sample Size

In a recent work,[21] the median survival time of euthyroid cases was nearly 12 years, the accrual interval was one year, and additional follow-up after the accrual interval of 15 years. If the true hazard ratio (relative risk) of hypothyroid cases relative to euthyroid cases is 2.45, 48 hypothyroid patients and 48 euthyroid (total 96) patients

Table 1 Baseline Data of the Two Studied Groups

	Euthyroid Group n=54	Hypothyroid Group n=53	p-value
Age (years)	46.3±5.8	49.6±6.6	0.007
Sex (male/female)	43/11	42/11	0.961
Diabetes Mellitus	17 (31.5%)	17 (32.1%)	0.947
Hypertension	8 (14.8%)	6 (11.3%)	0.592
Dyslipidemia	11 (20.4%)	13 (24.5%)	0.606
Smoking	14 (25.9%)	13 (24.5%)	0.868
Body mass index (kg/m^2)	27.9±2.9	26.9±3.6	0.153
Etiology			
HCV	23 (43.4%)	24 (44.4%)	
HBV	10 (18.9%)	8 (14.8%)	
Alcoholic liver disease	6 (11.3%)	6 (11.1%)	0.959
NAFLD	9 (17.0%)	7 (13.0%)	
Autoimmune liver disease	4 (7.5%)	4 (7.4%)	
Other etiology	2 (3.8%)	4 (7.4%)	
Donor Age (years)	29.9±5.1	31.0±6.0	0.304

Note: Data are summarized as mean±SD or Number (%).
Abbreviations: HCV, Hepatitis C virus; HBV, Hepatitis B virus; NAFLD, non-alcoholic fatty liver disease.

were needed to be able to reject the null hypothesis that the hypothyroid and euthyroid survival curves are equal with a power of 0.80. An additional 10% was added to compensate for expected losses; the total sample is 107 patients (53 per group). The Type-I error probability associated with this test of this null hypothesis is 0.05. The sample size was estimated using power and sample program version 3.1.2.

Statistical Methodology

Statistical analysis was performed using IBM© SPSS© Statistics version 22 (IBM© Corp., Armonk, NY, USA). Comparison between categorical variables was made by Chi-square test. Comparison between arms of numerical variables was done by *t*-test for normally distributed data and Mann–Whitney *U*-test for non-normally distributed data. Survival analysis was done using the Kaplan–Meier method. Comparison between two survival curves was done using Log rank test. Cox proportional hazard analysis was conducted to detect independent variables affecting survival. All tests were two-tailed. A p-value <0.05 was considered statistically significant.

Results

Follow-up started immediately post-transplantation. Cases were followed up for five years from the time of liver transplantation or till death.

The euthyroid and hypothyroid groups were comparable in all of the baseline characteristics except for the age of the patients (Table 1). The hypothyroid group was significantly older than the euthyroid group (p = 0.007). There were no considerable differences between the two groups in terms of all of the tumor characteristics and laboratory tests (Tables 2 and 3). TSH levels were significantly higher in the hypothyroid group, as this was the basis of group categorization.

The overall survival of the whole group at 48 months was 68.8%, while the DFS was 60.2% (Table 4). On univariate analysis overall survival was negatively affected by older age of the patients (p < 0.001) or the donor (p < 0.001), hypothyroidism (p = 0.008), HBV (p = 0.029), larger tumor size (p = 0.023), defective Milan criteria (p = 0.022), and recurrent gastrointestinal bleeding (p = 0.036). On multivariate analysis, the age of the patients and donors were the independent factors affecting overall survival (Table 5).

Table 2 Tumor Characteristics of the Two Studied Groups

	Euthyroid Group n=54	Hypothyroid Group n=53	p-value
Differentiation			
No viable tumor	11 (20.4%)	12 (22.6%)	0.793
Well and moderate	31 (57.4%)	27 (50.9%)	
Poorly and undifferentiated	12 (22.2%)	14 (26.4%)	
Tumor number			
Solitary	29 (53.7%)	24 (45.3%)	0.311
Two	14 (25.9%)	21 (39.6%)	
More than two	11 (20.4%)	8 (15.1%)	
Tumor diameter			
<3 cm	25 (46.3%)	24 (50.9%)	0.463
3-5 cm	21 (38.9%)	15 (28.3%)	
>5 cm	8 (14.8%)	11 (20.8%)	
Within Milan criteria	48 (88.9%)	46 (86.8%)	0.740
Vascular invasion	4 (7.4%)	6 (11.3%)	0.487
Recurrent Spontaneous peritonitis	11 (20.4%)	13 (24.5%)	0.606
Recurrent GI Bleeding	11 (20.4%)	12 (22.6%)	0.775
Recurrent encephalopathy	9 (16.7%)	8 (15.1%)	0.824
Resistant Ascites	6 (11.1%)	5 (9.4%)	0.775
Bridge treatment	19 (35.2%)	20 (37.7%)	0.784

Note: Data are summarized as Number (%).
Abbreviation: GI, gastrointestinal.

Table 3 Results of Laboratory Tests of the Two Studied Groups

	Euthyroid Group n=54	Hypothyroid Group n=53	p-value
TSH (mIU/L)	2.4±0.7	4.2±1.3	<0.001
Hemoglobin (gm/dL)	9.7±1.1	9.6±1.2	0.790
Total leukocytic count ($x10^3/mm^3$)	7.3±1.9	7.9±2.0	0.132
Platelets count ($x10^3/mm^3$)	187.0 (59.0–422.0)	176.0 (46.0–387.0)	0.803
Serum Albumin (mg/dL)	3.1±0.6	3.2±0.6	0.567
Total bilirubin (mg/dL)	2.0±0.4	2.0±0.5	0.436
AST (IU/L)	62.0 (34.0–87.0)	55.0 (32.0–110.0)	0.104
ALT (IU/L)	45.5 (25.0–78.0)	43.0 (24.0–84.0)	0.201
INR	1.7±0.3	1.8±0.3	0.457
Alpha fetoprotein (IU)	74.0 (12.0–453.0)	68.0 (10.0–365.0)	0.866
Glomerular filtration rate	87.1±11.4	86.8±10.5	0.870
MELD score	14.2±2.2	14.2±2.3	0.900

Note: Data are presented as mean±SD.
Abbreviations: TSH, Thyroid-stimulating Hormone; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; INR, The international normalized ratio; MELD, Model for End-stage Liver Disease.

Table 4 Cumulative Overall and Disease-Free Survival Proportion of the Two Studied Groups in Relation to the Possible Patient and Tumor Factors

		n	Cumulative OS at 48 Months (%)	p-value	Cumulative DFS at 48 Months (%)	p-value
Whole Group		107	68.8		60.2	
Age (years)						
≤ 50		77	81.7		69.7	
> 50		30	36.5	< 0.001	37.1	<0.001
Thyroid Status						
Euthyroid		54	79.9	0.008	71.9	0.005
Hypothyroid		53	57.5		47.8	
Donor Age (years)						
≤ 30		55	90.9	< 0.001	71.8	0.005
> 30		52	46.2		48.0	
Diabetes Mellitus	No	73	71.8		64.4	
	Yes	34	68.5	0.938	66.1	0.564
Hypertension	No	93	74.1		67.3	
	Yes	14	47.1	0.116	48.2	0.186
Dyslipidemia	No	83	71.8		65.6	
	Yes	24	66.7	0.410	53.6	0.286
HCV	No	60	70.9		65.6	
	Yes	47	65.8	0.880	51.1	0.620
HBV	No	89	75.3		67.5	
	Yes	18	46.3	0.029	39.5	0.019
Differentiation						
No viable tumor		23	68.6		59.6	
Well and moderate		26	58.9		43.8	
Poorly and undifferentiated		58	72.6	0.298	69.0	0.098
Tumor Number						
Single		53	64.7		59.0	
Multiple		54	72.6	0.626	59.3	0.509
Tumor Size						
≤ 3 cm		52	56.9		54.9	
> 3 cm		55	80.3	0.023	62.5	0.232
Within Milan	No	13	46.2		36.9	
	Yes	94	74.2	0.022	63.6	0.020
Vascular invasion	No	97	73.1		65.3	
	Yes	10	60.0	0.150	40.0	0.139
Bridge treatment	No	68	66.5		61.7	
	Yes	39	60.5	0.679	56.5	0.650
Recurrent Spontaneous peritonitis	No	83	74.0		63.8	
	Yes	24	60.0	0.248	50.6	0.314
Recurrent GIT Bleeding	No	84	74.7		64.3	
	Yes	23	48.5	0.036	46.4	0.087

(*Continued*)

Table 4 (Continued).

		n	Cumulative OS at 48 Months (%)	p-value	Cumulative DFS at 48 Months (%)	p-value
Recurrent Encephalopathy	No	90	72.8		61.7	
	Yes	17	58.8	0.096	52.9	0.222
Resistant Ascites	No	96	74.1		62.1	
	Yes	11	45.5	0.094	45.5	0.184

Abbreviations: HCV, hepatitis C virus; HBV, hepatitis B virus.

On univariate analysis disease-free survival was negatively affected by older age of the patients ($p < 0.001$) or the donor ($p = 0.005$), hypothyroidism ($p = 0.005$), HBV ($p = 0.019$), larger tumor size ($p = 0.023$), and defective Milan criteria ($p = 0.020$). On multivariate analysis, age of the patients, thyroid status and Milan criteria were the independent factors affecting DFS (Table 5).

Discussion

This study demonstrated that in patients with HCC undergoing liver transplantation, hypothyroidism is an independent factor that negatively affected disease-free but not overall survival. In these cases, the older age of the patients and liver donors were the independent factors worsening overall survival. Older age of the patients, hypothyroidism and Milan criteria were the independent factors affecting disease-free survival.

A great deal of research indicated a potential role of thyroid hormones in the pathogenesis of various cancer types. A previous study suggested that hyperthyroidism increases the hazard of some solid tumors, while hypothyroidism may decrease aggressiveness or delay the onset of malignancy.[22] This may be logical as thyroid hormones can exert a tumor-promoting effect. However, an opposite conclusion provoked by a recent systematic review of 14 studies concluded that hypothyroidism was linked to an increased risk of HCC and colorectal cancer and conversely decreased risk of prostate cancer.[23]

In a case-control study, Reddy et al suggested that hypothyroidism is an independent risk factor for developing HCC. This was based on a significantly higher likelihood of hypothyroidism in cases with HCC of unknown etiology than those with known etiology.[20] A larger case-control study, including 420 HCC patients, found that a history of hypothyroidism in women for more than ten years increased the risk of developing HCC. In contrast, this association was not observed in men.[16]

These findings enthused research on the molecular mechanisms through which hypothyroid status may promote tumorigenesis. Circulating thyroid hormones (THs) interact with thyroid hormone receptors (THRs) encoded by the TRα and TRβ genes. THs exert their effect via two mechanisms; stimulation of target gene expression through TRα and TRβ and a rapid, transcription-independent (nongenomic) effect.[24] These receptors are ligand-dependent transcription factors belonging to the nuclear receptors superfamily.[25] These receptors are reported to affect cell proliferation and malignant transformation. The liver is an important

Table 5 Multivariate Cox Regression Analysis for Independent Factors Affecting Overall and Disease-Free Survival on the Whole Studied Group (n=107)

	Regression Coefficient (B)	p-value	Hazard Ratio	95% Confidence Interval of Hazard Ratio
Overall Survival				
Recipient age	1.119	0.003	3.063	1.462–6.418
Donor age	1.611	0.001	5.009	1.874–13.389
Disease-free Survival				
Thyroid status	0.730	0.033	2.074	1.062–4.050
Recipient age	0.977	0.004	2.655	1.374–5.130
Within Milan criteria	0.925	0.023	2.521	1.137–5.593

Note: All variables mean that the higher values contribute to higher risk.

target organ of TH; hence, disruption of cellular TH-THRs signals is recognized to initiate liver diseases as chronic hepatitis and HCC.[17,26] For example, reduced expression of TRs is a common event in many human cancer.[16,27–29] Inactivating mutations in TRs that block access to the target genes has been detected in +70% of HCC patients.[30,31] Also, v-Erba, a mutant form of THRA missing the ability of ligand binding, is reported to cause HCC in transgenic mice.[32] In addition to maintaining hepatic homeostasis, the TH-THRs pathway acts as a tumor repressor in the liver.[17]

In the present work, hypothyroidism was an independent factor that impacted disease-free survival in those with HCC after liver transplantation. A plausible explanation for these findings was the data reported by Chi et al, who have shown that disruption of TH production induced marked progression of diethylnitrosamine (DEN)-induced HCC in a murine model. The administration of TH resulted in suppressing the carcinogenic process through the activation of autophagy.[17] Other studies in animal models indicated the critical role of normal autophagic flux in preventing HCC development.[33,34] Autophagy is a bulk degradation system of the impaired components of aggregated proteins in lysosomes to maintain cellular homeostasis.[35] In a rat model, the down-regulation of TRs, especially Trβ was an early event of the process of HCC carcinogenesis that heralds neoplastic transformation.[36]

In the current study, we took a step forward to investigate the impact of hypothyroidism on the outcome of HCC patients following liver transplantation. We found a negative effect of hypothyroidism on the survival of HCC patients, but why it was associated with worse outcomes is not clear. Findings of the previous studies focusing on the development of HCC might provide a reasonable explanation of the results of the current study. These studies indicated that hypothyroid status, whenever untreated, could promote HCC progression and consequently worsen overall and disease-free survival.

This study is not without limitations. The restricted sample size of a single-center study should be considered. Besides, the study did not investigate the mechanism by which hypothyroid status may exert its action.

Novelty of the Study

It is sensible to say that there is very scarce research that addressed the impact of hypothyroidism on patients with HCC after liver transplant. We have found only a single article indicating a poorer overall and recurrence-free survival in HCC patients having liver transplantation in the association of hypothyroidism.[21] Nonetheless, this study was a retrospective one, including 288 patients.

Notably, among the strengths of this work are the prospective nature and the reasonable number of cases with a pretty extended follow-up period.

Furthermore, the study provided epidemiological evidence that can be a nucleus for further research on the molecular basis of unsatisfactory outcomes associated with hypothyroidism.

We can conclude that hypothyroidism represents a risk factor for worse outcomes in HCC patients after liver transplantation. It was linked to poorer overall survival, and it independently worsens disease-free survival in these patients. More extensive multi-center studies are needed to confirm these findings, which may add a significant addition to the treatment of HCC patients after liver transplantation.

Disclosure

The authors declare that there is no conflicts of interest in this work.

References

1. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. *Lancet*. 2018;391(10127):1301–1314. doi:10.1016/S0140-6736(18)30010-2
2. Global Burden of Disease Liver Cancer Collaboration; Akinyemiju T, Abera S, Ahmed M, et al. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: results from the global burden of disease study 2015. *JAMA Oncol*. 2017;3(12):1683–1691. doi:10.1001/jamaoncol.2017.3055.
3. Ibrahim AS, Khaled HM, Mikhail NN, Baraka H, Kamel H. Cancer incidence in Egypt: results of the national population-based cancer registry program. *J Cancer Epidemiol*. 2014;2014:437971. doi:10.1155/2014/437971
4. Streba CT, Vere CC, Rogoveanu I, Dan Florescu N. Introductory chapter: etiology and pathogenesis of hepatocellular carcinoma. hepatocellular carcinoma - advances in diagnosis and treatment [Internet]. IntechOpen; 2018 [cited August 25, 2020]. Available from: https://www.intechopen.com/books/hepatocellular-carcinoma-advances-in-diagnosis-and-treatment/introductory-chapter-etiology-and-pathogenesis-of-hepatocellular-carcinoma. Accessed September 8, 2021.
5. Agosti P, Sabbà C, Mazzocca A. Emerging metabolic risk factors in hepatocellular carcinoma and their influence on the liver microenvironment. *Biochim Biophys Acta Mol Basis Dis*. 2018;1864(2):607–617. doi:10.1016/j.bbadis.2017.11.026
6. El Mahdy Korah T, Abd Elfatah Badr E, Mohamed Emara M, Ahmed Samy Kohla M, Gamal Saad Michael G.Relation between sex hormones and hepatocellular carcinoma. *Andrologia*. 2016;48(9):948–955. doi:10.1111/and.12536
7. Flamini MI, Uzair ID, Pennacchio GE, et al. Thyroid hormone controls breast cancer cell movement via integrin αV/β3/SRC/FAK/PI3-kinases. *Horm Cancer*. 2017;8(1):16–27. doi:10.1007/s12672-016-0280-3
8. Weingarten C, Jenudi Y, Tshuva RY, et al. The interplay between epithelial-mesenchymal transition (emt) and the thyroid hormones-αvβ3 axis in ovarian cancer. *Horm Cancer*. 2018;9(1):22–32. doi:10.1007/s12672-017-0316-3
9. Martínez-Iglesias O, García-Silva S, Regadera J, Aranda A. Hypothyroidism enhances tumor invasiveness and metastasis development. *PLoS One*. 2009;4(7):e6428. doi:10.1371/journal.pone.0006428

10. Oetting A, Yen PM. New insights into thyroid hormone action. *Best Pract Res Clin Endocrinol Metab*. 2007;21(2):193–208. doi:10.1016/j.beem.2007.04.004
11. Kadiyala R, Peter R, Okosieme OE. Thyroid dysfunction in patients with diabetes: clinical implications and screening strategies. *Int J Clin Pract*. 2010;64(8):1130–1139. doi:10.1111/j.1742-1241.2010.02376.x
12. Rhee CM, Brent GA, Kovesdy CP, et al. Thyroid functional disease: an under-recognized cardiovascular risk factor in kidney disease patients. *Nephrol Dial Transplant*. 2015;30(5):724–737. doi:10.1093/ndt/gfu024
13. Eshraghian A, Jahromi AH. Non-alcoholic fatty liver disease and thyroid dysfunction: a systematic review. *World J Gastroenterol*. 2014;20(25):8102–8109. doi:10.3748/wjg.v20.i25.8102
14. Pagadala MR, Zein CO, Dasarathy S, Yerian LM, Lopez R, McCullough AJ. Prevalence of hypothyroidism in non-alcoholic fatty liver disease. *Dig Dis Sci*. 2012;57(2):528–534. doi:10.1007/s10620-011-2006-2
15. Xu C, Xu L, Yu C, Miao M, Li Y. Association between thyroid function and non-alcoholic fatty liver disease in euthyroid elderly Chinese. *Clin Endocrinol*. 2011;75(2):240–246. doi:10.1111/j.1365-2265.2011.04016.x
16. Hassan MM, Kasab A, Li D, et al. Association between hypothyroidism and hepatocellular carcinoma: a case-control study in the United States. *Hepatology*. 2009;49(5):1563–1570. doi:10.1002/hep.22793
17. Chi H-C, Chen S-L, Tsai C-Y, et al. Thyroid hormone suppresses hepatocarcinogenesis via DAPK2 and SQSTM1-dependent selective autophagy. *Autophagy*. 2016;12(12):2271–2285. doi:10.1080/15548627.2016.1230583
18. Chi H-C, Chen S-L, Lin S-L, et al. Thyroid hormone protects hepatocytes from HBx-induced carcinogenesis by enhancing mitochondrial turnover. *Oncogene*. 2017;36(37):5274–5284. doi:10.1038/onc.2017.136
19. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology*. 2011;53(3):1020–1022. doi:10.1002/hep.24199
20. Reddy A, Dash C, Leerapun A, et al. Hypothyroidism: a possible risk factor for liver cancer in patients with no known underlying cause of liver disease. *Clin Gastroenterol Hepatol*. 2007;5(1):118–123. doi:10.1016/j.cgh.2006.07.011
21. Zhang N, Jin W, Zhou S, et al. Hypothyroidism is associated with worse outcomes of hepatocellular carcinoma patients after liver transplantation. *Cancer Med*. 2018;7(12):5870–5878. doi:10.1002/cam4.1797
22. Krashin E, Piekiełko-Witkowska A, Ellis M, Ashur-Fabian O. Thyroid hormones and cancer: a comprehensive review of preclinical and clinical studies. *Front Endocrinol*. 2019;10:59. doi:10.3389/fendo.2019.00059
23. Trodello C, Higgins S, Ahadiat O, Wysong A. Hypothyroidism as a risk factor for cancer: a systematic review and implications for future studies. *Cancer Sci Res Open Access*. 2017;4(2):1–7.
24. Gnoni GV, Rochira A, Leone A, Damiano F, Marsigliante S, Siculella L. 3,5,3′triiodo-L-thyronine induces SREBP-1 expression by non-genomic actions in human HEP G2 cells. *J Cell Physiol*. 2012;227(6):2388–2397. doi:10.1002/jcp.22974
25. Flamant F, Baxter JD, Forrest D, et al. The pharmacology and classification of the nuclear receptor superfamily: thyroid hormone receptors. *Pharmacol Rev Int Union Pharmacol*. 2006;58:705–711.
26. Lin Y-H, Huang Y-H, Wu M-H, et al. Thyroid hormone suppresses cell proliferation through endoglin-mediated promotion of p21 stability. *Oncogene*. 2013;32(33):3904–3914. doi:10.1038/onc.2013.5
27. Khan SR, Chaker L, Ruiter R, et al. thyroid function and cancer risk: the Rotterdam study. *J Clin Endocrinol Metab*. 2016;101(12):5030–5036. doi:10.1210/jc.2016-2104
28. Mondul AM, Weinstein SJ, Bosworth T, Remaley AT, Virtamo J, Albanes D. Circulating thyroxine, thyroid-stimulating hormone, and hypothyroid status and the risk of prostate cancer. *PLoS One*. 2012;7(10):e47730. doi:10.1371/journal.pone.0047730
29. Ortega-Olvera C, Ulloa-Aguirre A, Ángeles-llerenas A, et al. Thyroid hormones and breast cancer association according to menopausal status and body mass index. *Breast Cancer Res*. 2018;20(1):94. doi:10.1186/s13058-018-1017-8
30. Lin KH, Wu YH, Chen SL. Impaired interaction of mutant thyroid hormone receptors associated with human hepatocellular carcinoma with transcriptional Coregulators. *Endocrinology*. 2001;142(2):653–662. doi:10.1210/endo.142.2.7927
31. Chan I, Privalsky M. Thyroid hormone receptors mutated in liver cancer function as distorted antimorphs. *Oncogene*. 2006;25(25):3576–3588. doi:10.1038/sj.onc.1209389
32. Barlow C, Meister B, Lardelli M, Lendahl U, Vennström B. Thyroid abnormalities and hepatocellular carcinoma in mice transgenic for v-erbA. *EMBO J*. 1994;13(18):4241–4250. doi:10.1002/j.1460-2075.1994.tb06744.x
33. Takamura A, Komatsu M, Hara T, et al. Autophagy-deficient mice develop multiple liver tumors. *Genes Dev*. 2011;25(8):795–800. doi:10.1101/gad.2016211
34. Komatsu M. Liver autophagy: physiology and pathology. *J Biochem*. 2012;152(1):5–15. doi:10.1093/jb/mvs059
35. Kuma A, Hatano M, Matsui M, et al. The role of autophagy during the early neonatal starvation period. *Nature*. 2004;432(7020):1032–1036. doi:10.1038/nature03029
36. Frau C, Loi R, Petrelli A, et al. Local hypothyroidism favors the progression of preneoplastic lesions to hepatocellular carcinoma in rats. *Hepatology*. 2015;61(1):249–259. doi:10.1002/hep.27399