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Analysis of the Influence of Hypothyroidism on Liver Function Before Radioiodine Therapy among Patients with Differentiated Thyroid Cancer

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Abstract

Purpose The present study aimed to investigate the risk factors for hepatic dysfunction before radioiodine (RAI) therapy in patients with differentiated thyroid cancer (DTC). ***Methods*** We recruited 996 patients (314 males, 682 females; age, 45.07±12.98 years) who were postoperative of DTC. and divided them into two groups: one with hepatic dysfunction and one without. We compared changes in baseline data and traced liver function levels and other metabolic profiles between the groups. ***Result*** Overall, 31.6% of patients had hepatic dysfunction. Higher aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) was the most common abnormality (the prevalence rate was 47.5%). The percentages of mild and moderate hepatic dysfunction were 80.0% and 20.0%, respectively. Univariate analyses demonstrated that the most prominent risk factors for hepatic dysfunction (odds ratio [OR]=0.324-3.171, P<0.01) were male sex with levothyroxine discontinuation and free triiodothyronine (FT_3)< 2.01 pmol/L, free thyroxine (FT_4)<4.78 pmol/L, thyroid-stimulating hormone (TSH)>78.195 μIU/mL, total cholesterol (TC)>5.17 mmol/L , triglycerides (TG)>1.71 mmol/L and more than 21 days of THW . Multivariate analyses demonstrated that for males, FT_4<3.80 pmol/L and TG≥1.28 mmol/L were the most prominent risk factors. Patients with moderate hepatic dysfunction should be treated with hepatoprotective drugs. ***Conclusions*** Patients with minor hepatic dysfunction and ortholiposis are more likely to recover normal liver function. For males, FT_4 and TG levels tended to be associated with hepatic dysfunction, and the prognosis of hepatic dysfunction was closely related to the level of TG.

Strengths and limitations of this study:

Strengths: 1.in this study, we found that hepatic dysfunction is more likely to occur in male patients and patients with a THW time greater than 21 days, FT_3<2.01 pmol/L, FT_4<4.78 pmol/L, TSH>78.195 μIU/mL, TC>5.17 mmol/L, and TG>1.71 mmol/L. And lipid-lowering therapy is particularly important for DTC patients with hepatic dysfunction before ^{131}I therapy. 2.The results of this study may help nuclear physicians to make clinical treatment strategies of DTC patients.

Limitations: 1. since this was an uncontrolled retrospective study, the DTC patients involved in our study had hepatic dysfunction induced by hypothyroidism. Patients with liver diseases (such as autoimmune liver disease or viral hepatitis) or biliary tract diseases were excluded. However, corresponding testing was not universally performed to exclude these patients. 2. Additionally, we selected cases with complete data to perform our retrospective analysis. The exclusion of a few patients who were lost to follow-up might result in potential bias. 3.We could not collect LDL cholesterol measurements. For these reasons, further rigorous prospective studies are needed to confirm these preliminary findings.

Keywords: thyroid cancer, ^{131}I, high-dose radioiodine therapy, hepatic dysfunction, risk factors

1. Introduction

Radioiodine (RAI) therapy is a very important procedure to ablate normal thyroid remnant tissues and microscopic deposits ofdifferentiated thyroid carcinoma after thyroidectomy [1, 2]. As reported,RAI therapy was able to reduce the number of locoregional recurrences and to increase overall survival[3] [4]. In order to stimulate I^{131} uptake into the normal thyroid remnants and metastatic tissues of thyroid carcinoma when DTC patient undergoes RAI therapy, an elevated thyroid-stimulating hormone (thyrotropin, TSH) level is essential[5, 6]. Theclassic method of preparation for RAI therapy is thyroid hormone withdrawal (THW). It usually results in some physical or psychological side effects associated with hypothyroidism[7],such as general edema, constipation, and depression. Evidence indicates that hypothyroidism may affect liver function or structure directly[8, 9]. Therefore, identification of factors resulting in hepatic dysfunctio n is crucial. In the present study, we collected clinical data from 996 patients with differentiated thyroid cancer (DTC) to investigate risk factors for patients with hepatic dysfunction using a retrospective approach.

2. Materials and methods

2.1. Ethics statement

This study is a retrospective clinical study summarizing and analyzing a large amount of clinical data. The ethics committee of Tianjin Medical University General Hospital waived the need to obtain written informed consent from all patients. All clinical data used in this study were analyzed anonymously.

2.2. Patients and Public Involvement

The study included 996 patients (314 males, 682 females; age, 45.07±12.98 years)

who had undergone RAI therapy at our department from January 2012 to March 2018. The patients underwent complete or partial thyroidectomy performed by various surgeons. The patients agreed to receive RAI therapy and were informed about the traditional preparation method, THW. We used hepatitis virus markers, abdominal ultrasonography, echocardiography, and autoantibody and immunoglobulin subtype determination for patients with hepatic dysfunction to exclude other apparent causes of liver damage. Other causes included viral hepatitis, liver cirrhosis or biliary tract disease, chronic cardiac dysfunction and autoimmune liver disease[10].

2.3. Data collection and grouping

All RAI therapy regimens were conducted by the same nuclear medicine department following a standard protocol (2015 American Thyroid Association Management Guidelines). Data were recorded, including patient age (named X_1), sex (X_2), the time between surgery and ^{131}I therapy (X_3), the time of THW (X_4), the presence or absence of metastases (X_5), the presence of absence of Hashimoto's thyroiditis (X_6), serum free triiodothyronine (FT_3) (X_7), free thyroxine (FT_4) (X_8), TSH (X_9), thyroglobulin (Tg) (X_{10}), antithyroglobulin antibody (TgAb) (X_{11}), total cholesterol (TC) (X_{12}), and triglycerides (TG) (X_{13}). Meanwhile, liver function test results including aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total-value bilirubin (TBIL), and direct bilirubin (DBIL) were also collected. Hepatic dysfunction was diagnosed in accordance with the following criteria: ALT, AST or GGT<3 times the upper limit of normal (ULN), ALP<2 times the ULN and/or TBIL and DBIL<2.5 times the ULN were defined as mild hepatic dysfunction; 3 times the ULN <ALT or AST<20 times the ULN, 3 times the ULN< GGT<10 times the ULN, 2 times the ULN<ALP<5 times the ULN and/or 2.5 times the ULN <TBIL, and DBIL<5 time the ULN were defined as moderate hepatic dysfunction; and ALT or AST ≥20 times the ULN, GGT≥10 times the ULN, ALP ≥5 times the ULN and/or TBIL and DBIL≥5 times the ULN were defined as severe hepatic dysfunction[10].

2.4. Parameter assessments

Thyroid function tests were measured by chemiluminescence immunoassays (ADVIA

CENTAUR XP SIEMENS AG). Tg and TgAb were detected by the Immulite system (Immulite 2000 SIEMENS AG). Liver function indices were measured by colorimetry (Hitachi C7600 Japan). TC and TG levels were checked using an auto-analyzer enzymatically (Hitachi Model 7170 analyzer; Hitachi, Ltd., Tokyo, Japan). The dosage range of ^{131}I therapy was 3.7-7.4 GBq.

2.5. Patient follow-up

We measured the serum levels of thyroid parameters, serum lipids, and liver function indices of the 996 patients at 1, 2, 3, and 4 months after ^{131}I therapy to evaluate liver function.

2.6. Statistical analysis

A chi square test was used to analyze differences between ratios. To identify risk factors for hepatic dysfunction, we used a bivariate logistic regression model (univariate analysis) and stepwise logistic regression (multivariate analysis) with a variables with$p< 0.05$, and values <0.05 were considered statistically significant. The odds ratio(OR) was used to evaluate the risk factor. Statistical analysis was performed using SPSS (Statistical Package for Social Sciences) for Windows, version 20 (SPSS, Chicago, IL).

3. Results

3.1. Clinical features of hepatic dysfunction

Overall, 31.6% (315/996) of patients with DTC had hepatic dysfunction. Most patients with hepatic dysfunction had no obvious clinical symptoms except for abnormal liver function indices. The most common abnormality was elevated ALT and (or) AST, with a prevalence of 47.5%. The prevalence rates of mild, moderate, and severe hepatic dysfunction were 80.0% (252/315), 20.0% (63/315), and 0% (0/315), respectively.

3.2. Risk factors for hepatic dysfunction in DTC patients

In this paper, a binary logistic regression model was established two screen for relevant factors of hepatic dysfunction, and single-factor analysis and binary multivariate logistic regression analysis were performed. Patient characteristics were compared using bivariate logistic univariate regression analysis between the 2 groups (Table 1). The results showed that for male patients, the THW time, FT_3<2.01 pmol/L,

FT_4<4.78 pmol/L, TSH >78.195 μIU/mL, TC>5.17 mmol/L, and TG>1.71 mmol/L were closely associated with hepatic dysfunction (odds ratio [OR]: 0.324-3.171, all P<0.01).

Furthermore, we used multivariate logistic regression analysis to screen for relevant factors. In our study, we suggested the following assignments for independent variables: X_1=1 for age≤45 years and X_1=2 for age >45 years; X_2=1 for male sex and X_2=2 for female sex; X_3=1 if the time between total thyroidectomy and ^{131}I therapy was less than 3 months and X_3=2 if the time between total thyroidectomy and ^{131}I therapy was more than 3 months; X_4=1, 2, and 3 if the THW time was shorter than 3 weeks, 3-4 weeks, and longer than 4 weeks, respectively; X_5=1 for the presence of metastases and X_5=2 for the absence of metastases; X_6=1 for the presence of Hashimoto's thyroiditis and X_6=2 for the absence of Hashimoto's thyroiditis; X_7=1, 2, 3, and 4 for FT_3 levels lower than 1.60 pmol/L, 1.60-2.01 pmol/L, 2.01-2.37 pmol/L, and higher than 2.37 pmol/L, respectively; X_8=1, 2, 3, and 4 for FT_4 levels lower than 3.80 pmol/L, 3.80-4.78 pmol/L, 4.78-5.79 pmol/L, and higher than 5.79 pmol/L, respectively; X_9=1, 2, 3, and 4 for TSH levels lower than 57.01 μIU/mL, 57.01-78.20 μIU/mL, 78.20-101.84 μIU/mL, and higher than 101.84 μIU/mL, respectively; X_{10}=1, 2, 3, and 4 for Tg levels lower than 0.50 ng/mL, 0.50-2.64 ng/mL, 2.64-9.18 ng/mL, and higher than 9.18 ng/mL, respectively; X_{11}=1 for TgAb levels lower than 40 IU/mL and X_{11}=2 for TgAb levels higher than 40 IU/mL; X_{12}=1, 2, 3, and 4 for TC levels lower than 5.46 mmol/L, 5.46-6.27 mmol/L, 6.27-7.22 mmol/L, and higher than 6.27 mmol/L, respectively; and X_{13}=1, 2, 3, and 4 for TG levels lower than 1.28 mmol/L, 1.28-1.85 mmol/L, 1.85-2.76 mmol/L, and higher than 2.76 mmol/L, respectively. Resultant variable: Y=1 for patients with hepatic dysfunction, and Y=0 for patients without hepatic dysfunction. Forward stepwise regression analysis rejecting trends ultimately revealed that male sex, FT_4<3.80 pmol/L and TG≥1.28 mmol/L were independent risk factors predicting hepatic dysfunction in patients with DTC (Table 2).

3.3. Outcomes of hepatic dysfunction after ^{131}I therapy

The outcomes of hepatic dysfunction of varying degrees after ^{131}I therapy are

displayed in Table 3. The remission rate of patients at 1 month after ^{131}I therapy was 86.34% (272/315). Liver function test results returned to normal in 90.07% (227/252) of patients with mild hepatic dysfunction 1 month after ^{131}I therapy. Moreover, the remission rate among patients with moderate and severe hepatic dysfunction was 71.43% (45/63). Additionally, the remission rate of mild hepatic dysfunction was higher than that of moderate dysfunction (P<0.001).

Remission of hepatic dysfunction at 1 month after ^{131}I therapy is shown in Table 4. The liver function tests of 252 patients with mild hepatic dysfunction were evaluated at 1 month after ^{131}I therapy, the results of which returned to normal in 94.34% (50/53) of patients who were given hepatoprotective treatment (the treated group). Moreover, we found that the remission rate among patients in the untreated group was 88.94% (177/199). No remarkable difference in the remission rate was observed between the two groups (P=0.184).

63 patients with moderate hepatic dysfunction were treated with hepatoprotective therapy, and the remission rates among patients at 1 month, 2 months, and 3 months after ^{131}I therapy were 55.6% (35/63), 36.5% (23/63), and 7.9% (5/63) respectively. The time until liver function returned to normal in patients with moderate hepatic dysfunction was 1.8 months.

3.4. The correlation between serum TG and the remission rate of hepatic dysfunction in patients with DTC

A total of 559 patients had elevated serum TG before ^{131}I therapy, including 189 patients with hepatic dysfunction. All patients were divided into 2 subgroups based on their serum TG levels 1 month after ^{131}I therapy, subgroup 1: subjects with a normal TG level (141 patients), and subgroup 2: subjects with elevated TG (48 patients). Liver function tests results returned to normal in 92.90% (131/141) of the patients in subgroup 1. Moreover, the remission rate of the patients in subgroup 2 was 75% (36/48) (χ^2=5.382, P=0.02).

4. Discussion

- A complex relationship between the thyroid gland and the liver exists in both healthy and disease states[11]. Malik's research showed that thyroid dysfunction may affect liver function, [8]. A relationship has been suggested to exist between nonalcoholic fatty liver disease (NAFLD) and thyroid dysfunction[12]. Several studies conducted in some countries worldwide showed the relationship between levels of thyroid hormones and the incidence of NAFLD was inverse [13]. In clinical practice, we have found that hepatic dysfunction in DTC patients is common, and most of these patients have no obvious symptoms. The mechanism may be related to the following factors[11, 14]: (1) hypothyroidism may have features similar to those

of liver disease (pseudo-liver disease; such as myalgias, fatigue and muscle cramps in the presence of elevated aspartate aminotransferase from myopathy, coma; (2) hypothyroidism may interact liver structure or function directly; in experimental hypothyroidism, with the decrease of the activity of bilirubin UDP-glucuronyltransferase, bilirubin excretion is reduced; (3) hypothyroidism is related to cholestatic jaundice due to decreased bilirubin and bile excretion[15]; and (4) severe hypothyroidism is known to cause increased permeability of the vascular endothelium[16].

Our study demonstrated that 31.6% of DTC patients suffered from different degrees of hepatic dysfunction. All of these patients had mild or moderate liver injury. Additionally, an increase in ALT or AST was the most common abnormal indicator, and the prevalence was 47.5%. The findings are different from previous research data from Gokmen's group whose research showed that hypertriglyceridemia and a higher FT_3/FT_4 ratio are independent risk factors for NAFLD, however, hypothyroidism is not related to the condition directly [17]. However, their research subjects were patients with hypothyroidism, where hypothyroidism was defined only by a TSH level $\geq$ 4.1 mIU/L, and FT_3 and FT_4 levels were not included. The FT_3 and FT_4 levels of some patients were normal.

To explore the risk factors of hepatic dysfunction for DTC patients, we analyzed 13 related factors, such as age and sex, and found that male sex, a THW time greater than 21 days, FT_3<2.01 pmol/L, FT_4<4.78 pmol/L, TSH>78.195 μIU/mL, TC>5.17 mmol/L, and TG>1.71 mmol/L were risk factors for hepatic dysfunction in the univariate analysis (all P<0.01). Additionally, we found that male sex, FT_4<3.80 pmol/L and TG≥1.28 mmol/L were more closely associated with hepatic dysfunction in DTC patients in the multivariate logistic regression analysis (P<0.01). No studies related to our study on the risk factors of hepatic dysfunction for DTC patients were found.

In this study, we found that the remission rate of patients with mild hepatic dysfunction was significantly higher than that of patients with moderate hepatic dysfunction at 1 month after ^{131}I therapy. Additionally, the remission rate among patients with mild hepatic dysfunction was not significantly different between the treated group and the untreated group. We also found that the FT_4 level is associated with hepatic dysfunction, with more severe hypothyroidism corresponding to a greater impact on liver function. Patients with mild hepatic dysfunction may not be treated with hepatoprotective drugs because the remission rate of hepatic dysfunction at 1 month after ^{131}I therapy was not significantly different between the treated group and the untreated group. Recent studies revealed that with no liver damage, hepatic dysfunction associated with hypothyroidism can be reversed over several weeks with thyroxine replacement [18, 19].

Additionally, liver is the vital organ for cholesterol metabolism, thyroid hormones play an important role in hepatic lipid metabolism[8, 13]. Thyroid hormones increase the activity of lipid-lowering liver enzymes whichcan lead to a reduction in low-density lipoprotein levels [20]. Serum lipids also play an important role in liver function[19], which coincided with the results of our study. In our study,

hepatic function indices returned to normal at 1 month after ^{131}I therapy in 86.34% of the patients, the remission rate in patients with normal TG levels was significantly higher than that in the elevated TG group, and the time until liver dysfunction returned to normal in the patients suffering from hyperlipidemia and hepatic dysfunction was longer than that in the patients suffering from only hyperlipidemia. In other words, lipid-lowering therapy was very important for patients with hepatic dysfunction.

Conclusions

Hepatic dysfunction is more likely to occur in male patients and patients with a THW time greater than 21 days, FT_3<2.01 pmol/L, FT_4<4.78 pmol/L, TSH>78.195 μIU/mL, TC>5.17 mmol/L, and TG>1.71 mmol/L. Additionally, lipid-lowering therapy is particularly important for DTC patients with hepatic dysfunction before ^{131}I therapy. For DTC patients with hepatic dysfunction combined with dyslipidemia, lipid-lowering therapy is recommended, which is expected to shorten the remission time of hepatic dysfunction.

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Contribution to the Field Statement: An elevated TSH level is essential to stimulate ^{131}I uptake when patient with DTC undergoesRAI therapy. A number of patients suffer from general edema, constipation and so on, before RAI therapy with THW. Evidence reveals that hypothyroidism may have a direct effect on liver structure or function. We retrospectively collected clinical data from 996 patients with DTC to investigate risk factors of hepatic dysfunction in these patients. Patients with mild hepatic dysfunction and ortholiposis were found to have a higher likelihood of recovering normal liver function. For males, FT_4 and TG levels were more closely related to hepatic dysfunction, and the prognosis of hepatic dysfunction was closely associated with the level of TG.

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Table 1 Bivariate logistic univariate regression of the factors for DTC patients with hepatic dysfunction

Relevant factors		With hepatic dysfunction (n[%])	Without hepatic dysfunction (n[%])	B value	OR value	95%CI	P
Age	≤45	350(68.50%)	161(31.50%)	-1.011	1	0.744-1.321	0.934
	>45	331(68.25%)	154(31.75%)		1.011		
Sex	Male	158(50.97%)	152(49.03%)	-1.127	1	0.244-0.430	0.000
	Female	523(76.24%)	163(23.76%)		0.324		
the time between thyroidectomy and ^{131}I therapy	≤3 months	560(68.20%)	261(31.80%)	0.043	1	0.734-1.486	0.810
	>3 months	121(69.14%)	54(30.86%)		1.044		
Thyroid hormone withdrawal time	≤21 days	372(72.51%)	141(27.49%)	0.396	1	0.517-0.892	0.005
	>21 days	309(63.98%)	174(36.02%)		1.486		
Metastases	Negative	152(72.38%)	58(27.62%)	-0.242	1	0.561-1.100	0.160
	Positive	529(67.30%)	257(32.70%)		0.785		
Hashimoto's thyroiditis	Negative	595(67.85%)	282(32.15%)	-0.211	1	0.529-1.239	0.331
	Positive	86(72.27%)	33(27.73%)		0.810		
FT_3	<2.01*	316(63.71%)	180(36.29%)	0.432	1	1.177-2.016	0.002
	≥2.01	365(73.00%)	135(27.00%)		1.540		
FT_4	<4.78*	280(56.34%)	217(43.66%)	1.154	1	2.389-4.209	0.000
	≥4.78	401(80.36%)	98(19.64%)		3.171		
TSH	<78.195*	365(73.29%)	133(26.71%)	-0.458	1	0.483-0．828	0.001
	≥78.195	316(63.45%)	182(36.55%)		0.633		
Tg	<2.635*	346(69.48%)	152(30.52%)	-0.185	1	0.609-1.134	0.244
	≥2.635	335(67.27%)	163(32.73%)		0.831		

TgAb	≤40△	527(66.96%)	260(33.04%)	0.381	1	0.979-1.930	0.067
	>40	154(73.68%)	55(26.32%)		1.374		
TC	≤5.17△	129(75.44%)	42(24.56%)	0.758	1	1.615-2.822	0.000
	>5.17	552(66.90%)	273(33.10%)		2.135		
TG	≤1.71△	336(77.42%)	98(22.58%)	-0.418	1	0.451-0.960	0.03
	>1.71	344(61.54%)	215(38.46%)		0.658		

CI=confidence interval, OR=odds ratio, *median; △Upper limit of the normal value

Table 2 Bivariate logistic multivariate regression analysis of the factors for DTC patients with hepatic dysfunction

Causal variable	B	Standard error	Wald	df	P	EXP (B)	95%CI
X_2	-0.933	0.156	35.703	1	0.000	0.393	0.290-0.534
X_8 (FT_4)			62.291	3	0.000		
X_8 (2)	-0.347	0.193	3.249	1	0.071	0.707	0.485-1.031
X_8 (3)	-0.853	0.200	18.146	1	0.000	0.426	0.288-0.631
X_8 (4)	-1.789	0.239	55.817	1	0.000	0.167	0.105-0.267
X_{13}			15.195	3	0.002		
X_{13} (2)	0.325	0.225	2.072	1	0.150	1.383	0.889-2.152
X_{13} (3)	0.643	0.223	8.313	1	0.004	1.901	1.228-2.943
X_{13} (4)	0.787	0.219	12.784	1	0.000	2.197	1.429-3.376
Constant	-0.188	0.270	0.484	1	0.487	0.829	

Table 3 Outcomes of hepatic dysfunction of varying degrees after 1 month of ^{131}I therapy

Degree	n	Outcomes (n[%])	
		Remission	Nonremission
Mild	252	227 (90.07%)	25 (9.93%)
Moderate	63	45 (71.43%)	18 (28.57%)
χ^2		14.873	
p		0.000	

Table 4 Remission of hepatic dysfunction among patients given different treatments at 1 month after ^{131}I therapy

Group	n	Outcomes (n[%])	
		Remission	Nonremission
Treatment	53	50 (94.34%)	3 (5.66%)

No treatment	199	177 (88.94%)	22 (11.06%)
χ^2			1.765
p			0.184

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Analysis of the Influence of Hypothyroidism on Liver Function Before Radioiodine Therapy among Patients with Differentiated Thyroid Cancer

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Title page:

Analysis of the Influence of Hypothyroidism on Liver Function Before Radioiodine Therapy among Patients with Differentiated Thyroid Cancer

Running title: The Influence of hypothyroidism on the Liver Function in Patients with Differentiated Thyroid Cancer

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Key words: thyroid cancer, ^{131}I, radioiodine therapy, hepatic dysfunction, risk factors.

Conts:4364

Analysis of the Influence of Hypothyroidism on Liver Function Before Radioiodine Therapy among Patients with Differentiated Thyroid Cancer**Abstract**

Purpose The present study aimed to investigate the risk factors for hepatic dysfunction before radioiodine (RAI) therapy in patients with differentiated thyroid cancer (DTC). ***Methods*** We recruited 996 patients (314 males, 682 females; age, 45.07±12.98 years) who were postoperative of DTC, and divided them into two groups: one with hepatic dysfunction and one without. We compared changes in baseline data and traced liver function levels and other metabolic profiles between the groups. ***Result*** Overall, 31.6% of patients had hepatic dysfunction. Higher aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) was the most common abnormality (the prevalence rate was 47.5%). The percentages of mild and moderate hepatic dysfunction were 80.0% and 20.0%, respectively. Univariate analyses demonstrated that the most prominent risk factors for hepatic dysfunction (odds ratio [OR]=0.324-3.171, P<0.01) were male sex with levothyroxine discontinuation and free triiodothyronine (FT_3)< 2.01 pmol/L, free thyroxine (FT_4)<4.78 pmol/L, thyroid-stimulating hormone (TSH)>78.195 μIU/mL, total cholesterol (TC)>5.17 mmol/L , triglycerides (TG)>1.71 mmol/L and more than 21 days of thyroid hormone withdrawal (THW) . Multivariate analyses demonstrated that

for males, FT_4<3.80 pmol/L and TG≥1.28 mmol/L were the most prominent risk factors. ***Conclusions*** Patients with minor hepatic dysfunction and ortholiposis are more likely to recover normal liver function. Patients with moderate hepatic dysfunction should be treated with hepatoprotective drugs.For males, FT_4 and TG levels tended to be associated with hepatic dysfunction, and the prognosis of hepatic dysfunction was closely related to the level of TG.

Strengths and limitations of this study:

Strengths: 1.in this study, we found that hepatic dysfunction is more likely to occur in male patients and patients with a THW time greater than 21 days, FT_3<2.01 pmol/L, FT_4<4.78 pmol/L, TSH>78.195 μIU/mL, TC>5.17 mmol/L, and TG>1.71 mmol/L. And lipid-lowering therapy is particularly important for DTC patients with hepatic dysfunction before ^{131}I therapy. 2.The results of this study may help nuclear physicians to make clinical treatment strategies of DTC patients.

Limitations: 1. Since this was an uncontrolled retrospective study, the DTC patients involved in our study had hepatic dysfunction induced by hypothyroidism. Patients with liver diseases (such as autoimmune liver disease or viral hepatitis) or biliary tract diseases were excluded. However, corresponding testing was not universally performed to exclude these patients. 2. Additionally, we selected cases with complete data to perform our retrospective analysis. The exclusion of a few patients who were lost to follow-up might result in potential bias. 3.We could not collect LDL cholesterol measurements. Obesity is a very important metabolic risk factor that contributes to liver and thyroid dysfunction. It would be very helpful if we analysis of the influence of overweight and/or obese on hypothyroidism and Liver Function. For these reasons, further rigorous prospective studies are needed to confirm these preliminary findings.

Keywords: thyroid cancer, ^{131}I, high-dose radioiodine therapy, hepatic dysfunction, risk factors

1. Introduction

Radioiodine (RAI) therapy is a very important procedure to ablate normal thyroid remnant tissues and microscopic deposits of differentiated thyroid carcinoma (DTC) after thyroidectomy [1, 2]. As reported, RAI therapy was able to reduce the number of locoregional recurrences and to increase overall survival of the American Thyroid Association(ATA) intermediate-risk and high risk DTC patients [3] [4]. In order to stimulate I^{131} uptake into the normal thyroid remnants and metastatic tissues of thyroid carcinoma when DTC patient undergoes RAI therapy, an elevated thyroid-stimulating hormone (thyrotropin, TSH) level is essential[5, 6]. Theclassic method of preparation for RAI therapy is thyroid hormone withdrawal (THW). It usually results in some physical or psychological side effects associated with hypothyroidism[7], such as general edema, constipation, and depression. Evidence indicates that hypothyroidism may affect liver function or structure directly[8, 9].

Therefore, identification of factors resulting in hepatic dysfunction is crucial. In the present study, we collected clinical data from 996 patients with DTC to investigate risk factors for patients with hepatic dysfunction using a retrospective approach.

2. Materials and methods

2.1. Ethics statement

This study is a retrospective clinical study summarizing and analyzing a large amount of clinical data. The ethics committee of Tianjin Medical University General Hospital waived the need to obtain written informed consent from all patients. All clinical data used in this study were analyzed anonymously.

2.2. Patients and Public Involvement

The study included 996 patients (314 males, 682 females; age, 45.07±12.98 years) who had undergone RAI therapy at our department from January 2012 to March 2018. The patients underwent complete or partial thyroidectomy performed by various surgeons. The patients agreed to receive RAI therapy and were informed about the traditional preparation method, THW. We used hepatitis virus markers, abdominal ultrasonography, echocardiography, and autoantibody and immunoglobulin subtype determination for patients with hepatic dysfunction to exclude other apparent causes of liver damage. Other causes included viral hepatitis, liver cirrhosis or biliary tract disease, chronic cardiac dysfunction and autoimmune liver disease, liver steatosis, hyperlipoidemia, etc[10].

2.3. Data collection and grouping

All RAI therapy regimens were conducted by the same nuclear medicine department following a standard protocol (2015 American Thyroid Association Management Guidelines). Data were recorded, including patient age (named X_1), sex (X_2), the time between surgery and ^{131}I therapy (X_3), the time of THW (X_4), the presence or absence of metastases (lymph node metastasis or lung metastases), (X_5), the presence of absence of Hashimoto's thyroiditis (X_6), serum free triiodothyronine (FT_3) (X_7), free thyroxine (FT_4) (X_8), TSH (X_9), thyroglobulin (Tg) (X_{10}), antithyroglobulin antibody (TgAb) (X_{11}), total cholesterol (TC) (X_{12}), and triglycerides (TG) (X_{13}). Meanwhile, liver function test results including aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total-value bilirubin (TBIL), and direct bilirubin (DBIL) were also collected. Hepatic dysfunction was diagnosed in accordance with the following criteria: the upper limit of normal (ULN) <ALT, AST or GGT<3 times ULN, the ULN<ALP<2 times the ULN and/or TBIL and the ULN<DBIL<2.5 times the ULN were defined as

mild hepatic dysfunction; 3 times the ULN <ALT or AST<20 times the ULN, 3 times the ULN< GGT<10 times the ULN, 2 times the ULN<ALP<5 times the ULN and/or 2.5 times the ULN <TBIL, and DBIL<5 time the ULN were defined as moderate hepatic dysfunction; and ALT or AST ≥20 times the ULN, GGT≥10 times the ULN, ALP ≥5 times the ULN and/or TBIL and DBIL≥5 times the ULN were defined as severe hepatic dysfunction[10].

2.4. Parameter assessments

Thyroid function tests were measured by chemiluminescence immunoassays (ADVIA CENTAUR XP SIEMENS AG). Tg and TgAb were detected by the Immulite system (Immulite 2000 SIEMENS AG). Liver function indices were measured by colorimetry (Hitachi C7600 Japan). TC and TG levels were checked using an auto-analyzer enzymatically (Hitachi Model 7170 analyzer; Hitachi, Ltd., Tokyo, Japan). The dosage range of ^{131}I therapy was 3.7-7.4 GBq.

2.5. Patient follow-up

We measured the serum levels of thyroid parameters, serum lipids, and liver function indices of the 996 patients at 1, 2, 3, and 4 months after ^{131}I therapy to evaluate liver function.

2.6. Statistical analysis

A chi square test was used to analyze differences between ratios. To identify risk factors for hepatic dysfunction, we used a bivariate logistic regression model (univariate analysis) and stepwise logistic regression (multivariate analysis) with a variables with$p< 0.05$, and values <0.05 were considered statistically significant. The odds ratio(OR) was used to evaluate the risk factor. Statistical analysis was performed using SPSS (Statistical Package for Social Sciences) for Windows, version 20 (SPSS, Chicago, IL).

3. Results

3.1. Clinical features of hepatic dysfunction

Overall, 31.6% (315/996) of patients with DTC had hepatic dysfunction. Most patients with hepatic dysfunction had no obvious clinical symptoms except for abnormal liver function indices. The most common abnormality was elevated ALT and (or) AST, with a prevalence of 47.5%. The prevalence rates of mild, moderate, and severe hepatic dysfunction were 80.0% (252/315), 20.0% (63/315), and 0% (0/315), respectively.

3.2. Risk factors for hepatic dysfunction in DTC patients

In this paper, a binary logistic regression model was established for relevant factors of hepatic dysfunction, and single-factor analysis and binary multivariate logistic regression analysis were performed. Patient characteristics were compared using bivariate logistic univariate regression analysis between the 2 groups (Table 1). In the metastase group, the number of patients with hepatic dysfunction and lymph node metastasis or lung metastases were 508 and 21 respectively; and the number of patients without hepatic dysfunction were 245 (with lymph node metastasis) and 12 (with lung metastases) respectively. The results showed that for male patients, the THW time, FT_3<2.01 pmol/L, FT_4<4.78 pmol/L, TSH >78.195 μIU/mL, TC>5.17 mmol/L, and TG>1.71 mmol/L were closely associated with hepatic dysfunction (odds ratio [OR]: 0.324-3.171, all P<0.01).

Furthermore, we used multivariate logistic regression analysis to screen for relevant factors. In our study, we suggested the following assignments for independent variables: X_1=1 for age≤45 years and X_1=2 for age >45 years; X_2=1 for male sex and X_2=2 for female sex; X_3=1 if the time between total thyroidectomy and ^{131}I therapy was less than 3 months and X_3=2 if the time between total thyroidectomy and ^{131}I therapy was more than 3 months; X_4=1, 2, and 3 if the THW time was shorter than 3 weeks, 3-4 weeks, and longer than 4 weeks, respectively; X_5=1 for the presence of metastases and X_5=2 for the absence of metastases; X_6=1 for the presence of Hashimoto's thyroiditis and X_6=2 for the absence of Hashimoto's thyroiditis; X_7=1, 2, 3, and 4 for FT_3 levels lower than 1.60 pmol/L, 1.60-2.01 pmol/L, 2.01-2.37 pmol/L, and higher than 2.37 pmol/L, respectively; X_8=1, 2, 3, and 4 for FT_4 levels lower than 3.80 pmol/L, 3.80-4.78 pmol/L, 4.78-5.79 pmol/L, and higher than 5.79 pmol/L, respectively; X_9=1, 2, 3, and 4 for TSH levels lower than 57.01 μIU/mL, 57.01-78.20 μIU/mL, 78.20-101.84 μIU/mL, and higher than 101.84 μIU/mL, respectively; X_{10}=1, 2, 3, and 4 for Tg levels lower than 0.50 ng/mL, 0.50-2.64 ng/mL, 2.64-9.18 ng/mL, and higher than 9.18 ng/mL, respectively; X_{11}=1 for TgAb levels lower than 40 IU/mL and X_{11}=2 for TgAb levels higher than 40 IU/mL; X_{12}=1, 2, 3, and 4 for TC levels lower than 5.46 mmol/L, 5.46-6.27 mmol/L, 6.27-7.22 mmol/L, and higher

than 6.27 mmol/L, respectively; and X_{13}=1, 2, 3, and 4 for TG levels lower than 1.28 mmol/L, 1.28-1.85 mmol/L, 1.85-2.76 mmol/L, and higher than 2.76 mmol/L, respectively. Resultant variable: Y=1 for patients with hepatic dysfunction, and Y=0 for patients without hepatic dysfunction. Forward stepwise regression analysis rejecting trends ultimately revealed that male sex, FT_4<3.80 pmol/L and TG≥1.28 mmol/L were independent risk factors predicting hepatic dysfunction in patients with DTC (Table 2).

3.3. Outcomes of hepatic dysfunction after ^{131}I therapy

The outcomes of hepatic dysfunction of varying degrees after ^{131}I therapy are displayed in Table 3. The remission rate of patients at 1 month after ^{131}I therapy was 86.34% (272/315). Liver function test results returned to normal in 90.07% (227/252) of patients with mild hepatic dysfunction 1 month after ^{131}I therapy. Moreover, the remission rate among patients with moderate and severe hepatic dysfunction was 71.43% (45/63). Additionally, the remission rate of mild hepatic dysfunction was higher than that of moderate dysfunction (P<0.001).

Remission of hepatic dysfunction at 1 month after ^{131}I therapy is shown in Table 4. The liver function tests of 252 patients with mild hepatic dysfunction were evaluated at 1 month after ^{131}I therapy, the results of which returned to normal in 94.34% (50/53) of patients who were given hepatoprotective treatment [oral bicyclol tablets, Bicyclol 25 mg/tablet, Beijing Union Pharmaceutical Factory, Beijing, China, at a total daily dose of 75mg (25mg three times daily), the treated group]. Moreover, we found that the remission rate among patients in the untreated group was 88.94% (177/199). No remarkable difference in the remission rate was observed between the two groups (P=0.184).

63 patients with moderate hepatic dysfunction were treated with hepatoprotective therapy [oral bicyclol tablets, at a total daily dose of 150mg (50mg three times daily)], and the remission rates among patients at 1 month, 2 months, and 3 months after ^{131}I therapy were 55.6% (35/63), 36.5% (23/63), and 7.9% (5/63) respectively. The time until liver function returned to normal in patients with moderate hepatic dysfunction was 1.8 months.

3.4. The correlation between serum TG and the remission rate of hepatic dysfunction in patients with DTC

A total of 559 patients had elevated serum TG before ^{131}I therapy, including 189 patients with hepatic dysfunction(76 males,113 females). All patients were divided into 2 subgroups based on their serum TG levels 1 month after ^{131}I therapy, subgroup 1: subjects with a normal TG level (141 patients), and subgroup 2: subjects with elevated TG (48 patients). Liver function tests results returned to normal in 92.90% (131/141) of the patients in subgroup 1. Moreover, the remission rate of the patients in subgroup 2 was 75% (36/48) (χ^2=5.382, P=0.02). **4. Discussion**

A complex relationship between the thyroid gland and the liver exists in both healthy and disease states[11]. Maliks research showed that thyroid dysfunction may affect liver function, [8]. A relationship has been suggested to exist between nonalcoholic fatty liver disease (NAFLD) and thyroid dysfunction[12]. Several studies conducted in some countries worldwide showed the relationship between levels of thyroid hormones and the incidence of NAFLD was inverse [13]. In clinical practice, we have found that hepatic dysfunction in DTC patients is common, and most of these patients have no obvious symptoms. The mechanism may be related to the following factors[11, 14]: (1) hypothyroidism may have features similar to those of liver disease (pseudo-liver disease; such as myalgias, fatigue and muscle cramps in the presence of elevated aspartate aminotransferase from myopathy, coma; (2) hypothyroidism may interact liver structure or function directly; in experimental hypothyroidism, with the decrease of the activity of bilirubin UDP-glucuronyltransferase, bilirubin excretion is reduced; (3) hypothyroidism is related to cholestatic jaundice due to decreased bilirubin and bile excretion[15]; and (4) severe hypothyroidism is known to cause increased permeability of the vascular endothelium[16].

Our study demonstrated that 31.6% of DTC patients suffered from different degrees of hepatic dysfunction. All of these patients had mild or moderate liver injury. Additionally, an increase in ALT or AST was the most common abnormal indicator, and the prevalence was 47.5%. The findings are different from previous research data from Gokmen's group whose research showed that hypertriglyceridemia and a higher FT_3/FT_4 ratio are independent risk factors for NAFLD, however, hypothyroidism is not related to the condition directly [17]. However, their research subjects were patients with hypothyroidism, where hypothyroidism was defined only by a TSH level $\geq$ 4.1 mIU/L, and FT_3 and FT_4 levels were not included. The FT_3 and FT_4 levels of some patients were normal.

To explore the risk factors of hepatic dysfunction for DTC patients, we analyzed 13 related factors, such as age and sex, and found that male sex, a THW time greater than 21 days, FT_3<2.01 pmol/L, FT_4<4.78 pmol/L, TSH>78.195 μIU/mL, TC>5.17 mmol/L, and TG>1.71 mmol/L were risk factors for hepatic dysfunction in the univariate analysis (all P<0.01). Additionally, we found that male sex, FT_4<3.80 pmol/L and TG≥1.28 mmol/L were more closely associated with hepatic dysfunction in DTC patients in the multivariate logistic regression analysis (P<0.01). No studies related to our study on the risk factors of hepatic dysfunction for DTC patients were found.

In this study, we found that the remission rate of patients with mild hepatic

dysfunction was significantly higher than that of patients with moderate hepatic dysfunction at 1 month after ^{131}I therapy. Additionally, the remission rate among patients with mild hepatic dysfunction was not significantly different between the treated group and the untreated group. We also found that the FT_4 level is associated with hepatic dysfunction, with more severe hypothyroidism corresponding to a greater impact on liver function. Patients with mild hepatic dysfunction may not be treated with hepatoprotective drugs because the remission rate of hepatic dysfunction at 1 month after ^{131}I therapy was not significantly different between the treated group and the untreated group. Recent studies revealed that with no liver damage, hepatic dysfunction associated with hypothyroidism can be reversed over several weeks with thyroxine replacement [18, 19].

Additionally, liver is the vital organ for cholesterol metabolism, thyroid hormones play an important role in hepatic lipid metabolism[8, 13]. Thyroid hormones increase the activity of lipid-lowering liver enzymes which can lead to a reduction in low-density lipoprotein levels [20]. Serum lipids also play an important role in liver function[19], which coincided with the results of our study. In our study, hepatic function indices returned to normal at 1 month after ^{131}I therapy in 86.34% of the patients, the remission rate in patients with normal TG levels was significantly higher than that in the elevated TG group, and the time until liver dysfunction returned to normal in the patients suffering from hyperlipidemia and hepatic dysfunction was longer than that in the patients suffering from only hyperlipidemia. In other words, lipid-lowering therapy was very important for patients with hepatic dysfunction.

Conclusions

Hepatic dysfunction is more likely to occur in male patients and patients with a THW time greater than 21 days, FT_3<2.01 pmol/L, FT_4<4.78 pmol/L, TSH>78.195 μIU/mL, TC>5.17 mmol/L, and TG>1.71 mmol/L. Additionally, lipid-lowering therapy is particularly important for DTC patients with hepatic dysfunction before ^{131}I therapy. For DTC patients with hepatic dysfunction combined with dyslipidemia, lipid-lowering therapy is recommended, which is expected to shorten the remission time of hepatic dysfunction.

Contribution to the Field Statement: An elevated TSH level is essential to stimulate ^{131}I uptake when patient with DTC undergoesRAI therapy. A number of patients suffer from general edema, constipation and so on, before RAI therapy with THW. Evidence reveals that hypothyroidism may have a direct effect on liver structure or function. We retrospectively collected clinical data from 996 patients with DTC to investigate risk factors of hepatic dysfunction in these patients. Patients with mild hepatic dysfunction and ortholiposis were found to have a higher likelihood of recovering normal liver function. For males, FT_4 and TG levels were more closely related to hepatic dysfunction, and the prognosis of hepatic dysfunction was closely associated with the level of TG.

Contributorship Statement： Yanhui Ji and Renfei Wang contributed to the conception and design of the study. Yanhui Ji, Wei Zheng, Jian Tan, and Cailan Wu

assisted with data acquisition. Yanhui Ji , Zhaowei Meng, and Renfei Wang conducted the statistical analyses and drafted the manuscript. Jian Tan, Zhaowei Meng critically revised the manuscript. All authors read and approved the final manuscript and agree to be accountable for all aspects of the research in ensuring that the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interests

There are no competing interests for any author

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Data sharing statement

The datasets used during the present study are available from the corresponding author upon reasonable request.

Ethical Approval statement

The studies involving human participants were reviewed and approved by Ethical Committee of Tianjin Medical University General Hospital (NO. IRB2020-WZ-001). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

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Table 1 Bivariate logistic univariate regression of the factors for DTC patients with hepatic dysfunction

Relevant factors	With hepatic	Without hepatic	B value	OR	95%CI	P

		dysfunction (n[%])	dysfunction (n[%])		value		
Age	≤45	350(68.50%)	161(31.50%)	-1.011	1	0.744-1.321	0.934
	>45	331(68.25%)	154(31.75%)		1.011		
Sex	Male	158(50.97%)	152(49.03%)	-1.127	1	0.244-0.430	0.000
	Female	523(76.24%)	163(23.76%)		0.324		
the time between thyroidectomy and ^{131}I therapy	≤3 months	560(68.20%)	261(31.80%)	0.043	1	0.734-1.486	0.810
	>3 months	121(69.14%)	54(30.86%)		1.044		
Thyroid hormone withdrawal time	≤21 days	372(72.51%)	141(27.49%)	0.396	1	0.517-0.892	0.005
	>21 days	309(63.98%)	174(36.02%)		1.486		
Metastases	Negative	152(72.38%)	58(27.62%)	-0.242	1	0.561-1.100	0.160
	Positive	529(67.30%)	257(32.70%)		0.785		
Hashimoto's thyroiditis	Negative	595(67.85%)	282(32.15%)	-0.211	1	0.529-1.239	0.331
	Positive	86(72.27%)	33(27.73%)		0.810		
FT_3	<2.01*	316(63.71%)	180(36.29%)	0.432	1	1.177-2.016	0.002
	≥2.01	365(73.00%)	135(27.00%)		1.540		
FT_4	<4.78*	280(56.34%)	217(43.66%)	1.154	1	2.389-4.209	0.000
	≥4.78	401(80.36%)	98(19.64%)		3.171		
TSH	<78.195*	365(73.29%)	133(26.71%)	-0.458	1	0.483-0．828	0.001
	≥78.195	316(63.45%)	182(36.55%)		0.633		
Tg	<2.635*	346(69.48%)	152(30.52%)	-0.185	1	0.609-1.134	0.244
	≥2.635	335(67.27%)	163(32.73%)		0.831		
TgAb	≤40$^{\Delta}$	527(66.96%)	260(33.04%)	0.381	1	0.979-1.930	0.067
	>40	154(73.68%)	55(26.32%)		1.374		
TC	≤5.17$^{\Delta}$	129(75.44%)	42(24.56%)	0.758	1	1.615-2.822	0.000
	>5.17	552(66.90%)	273(33.10%)		2.135		
TG	≤1.71$^{\Delta}$	336(77.42%)	98(22.58%)	-0.418	1	0.451-0.960	0.03
	>1.71	344(61.54%)	215(38.46%)		0.658		

CI=confidence interval, OR=odds ratio, *median; $^{\Delta}$Upper limit of the normal value

Table 2 Bivariate logistic multivariate regression analysis of the factors for DTC patients with hepatic dysfunction

Causal variable	B	Standard error	Wald	df	P	EXP (B)	95%CI
X_2	-0.933	0.156	35.703	1	0.000	0.393	0.290-0.534

X_8 (FT_4)			62.291	3	0.000		
X_8 (2)	-0.347	0.193	3.249	1	0.071	0.707	0.485-1.031
X_8 (3)	-0.853	0.200	18.146	1	0.000	0.426	0.288-0.631
X_8 (4)	-1.789	0.239	55.817	1	0.000	0.167	0.105-0.267
X_{13}			15.195	3	0.002		
X_{13} (2)	0.325	0.225	2.072	1	0.150	1.383	0.889-2.152
X_{13} (3)	0.643	0.223	8.313	1	0.004	1.901	1.228-2.943
X_{13} (4)	0.787	0.219	12.784	1	0.000	2.197	1.429-3.376
Constant	-0.188	0.270	0.484	1	0.487	0.829	

Table 3 Outcomes of hepatic dysfunction of varying degrees after 1 month of ^{131}I therapy

Degree	n	Outcomes (n[%])	
		Remission	Nonremission
Mild	252	227 (90.07%)	25 (9.93%)
Moderate	63	45 (71.43%)	18 (28.57%)
χ^2		14.873	
p		0.000	

Table 4 Remission of hepatic dysfunction among patients given different treatments at 1 month after ^{131}I therapy

Group	n	Outcomes (n[%])	
		Remission	Nonremission
Treatment	53	50 (94.34%)	3 (5.66%)
No treatment	199	177 (88.94%)	22 (11.06%)
χ^2		1.765	
p		0.184	

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A Retrospective Study of The Influence of Hypothyroidism on Liver Function Before Radioiodine Therapy in China: A Comparison Analysis based on Patients with Differentiated Thyroid Cancer

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A Retrospective Study of The Influence of Hypothyroidism on Liver Function Before Radioiodine Therapy in China: A Comparison Analysis based on Patients with Differentiated Thyroid Cancer

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Abstract

Purpose The present study aimed to investigate the risk factors for hepatic dysfunction before radioiodine (RAI) therapy in patients with differentiated thyroid cancer (DTC). ***Methods*** We recruited 996 patients (314 males, 682 females; age, 45.07±12.98 years) who were postoperative of DTC, and divided them into two groups: one with hepatic dysfunction and one without. We compared changes in baseline data and traced liver function levels and other metabolic profiles between the groups. ***Result*** Overall, 31.6% of patients had hepatic dysfunction. Higher aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) was the most common abnormality (the prevalence rate was 47.5%). The percentages of mild and moderate hepatic dysfunction were 80.0% and 20.0%, respectively. Univariate analyses demonstrated that the most prominent risk factors for hepatic dysfunction (odds ratio [OR]=0.324-3.171, P<0.01) were male sex with levothyroxine discontinuation and free triiodothyronine (FT_3)< 2.01 pmol/L, free thyroxine (FT_4)<4.78 pmol/L, thyroid-stimulating hormone (TSH)>78.195 μIU/mL, total cholesterol (TC)>5.17 mmol/L , triglycerides (TG)>1.71 mmol/L and more than 21 days of thyroid hormone withdrawal (THW) . Multivariate analyses demonstrated that for males, FT_4<3.80 pmol/L and TG≥1.28 mmol/L were the most prominent risk

factors. ***Conclusions*** Patients with minor hepatic dysfunction and ortholiposis are more likely to recover normal liver function. Patients with moderate hepatic dysfunction should be treated with hepatoprotective drugs.For males, FT_4 and TG levels tended to be associated with hepatic dysfunction, and the prognosis of hepatic dysfunction was closely related to the level of TG.

Strengths and limitations of this study:

Strengths:The results of this study may help nuclear physicians to make clinical treatment strategies of DTC patients.

Limitations: performed to exclude these patients.

1. We selected cases with complete data to perform our retrospective analysis, the exclusion of a few patients who were lost to follow-up might result in potential bias.

2.We could not collect LDL cholesterol measurements.

3.Obesity is a important metabolic risk factorof liver and thyroid dysfunction, and it would be helpful if we analysis of the influence of it in our study

For these reasons, further rigorous prospective studies are needed to confirm these preliminary findings.

Keywords: thyroid cancer, ^{131}I, high-dose radioiodine therapy, hepatic dysfunction, risk factors

1. Introduction

Radioiodine (RAI) therapy is a very important procedure to ablate normal thyroid remnant tissues and microscopic deposits of differentiated thyroid carcinoma (DTC) after thyroidectomy [1]. As reported, RAI therapy was able to reduce the number of locoregional recurrences and to increase overall survival of the American Thyroid Association(ATA) intermediate-risk and high risk DTC patients [2 3]. In order to stimulate I^{131} uptake into the normal thyroid remnants and metastatic tissues of thyroid carcinoma when DTC patient undergoes RAI therapy, an elevated thyroid-stimulating hormone (thyrotropin, TSH) level is essential[4]. Theclassic method of preparation for RAI therapy is thyroid hormone withdrawal (THW). It usually results in some physical or psychological side effects associated with hypothyroidism[5], such as general edema, constipation, and depression. Evidence indicates that hypothyroidism may affect liver function or structure directly[6]. Therefore, identification of factors resulting in hepatic dysfunction is crucial. In the present study, we collected clinical data from 996 patients with DTC to investigate risk factors for patients with hepatic dysfunction using a retrospective approach.

2. Materials and methods

2.1. Ethics statement

This study is a retrospective clinical study summarizing and analyzing a large amount of clinical data. The ethics committee of Tianjin Medical University General Hospital waived the need to obtain written informed consent from all patients. All clinical data

used in this study were analyzed anonymously.

2.2. Participants or Criteria selection

The study included 996 patients (314 males, 682 females; age, 45.07±12.98 years) who had undergone RAI therapy at our department from January 2012 to March 2018. The patients underwent complete or partial thyroidectomy performed by various surgeons. The patients agreed to receive RAI therapy and were informed about the traditional preparation method, THW. We used hepatitis virus markers, abdominal ultrasonography, echocardiography, and autoantibody and immunoglobulin subtype determination for patients with hepatic dysfunction to exclude other apparent causes of liver damage. Other causes included viral hepatitis, liver cirrhosis or biliary tract disease, chronic cardiac dysfunction and autoimmune liver disease, liver steatosis, hyperlipoidemia, etc[7].

2.3. Data collection and grouping

All RAI therapy regimens were conducted by the same nuclear medicine department following a standard protocol (2015 American Thyroid Association Management Guidelines). Data were recorded, including patient age (named X_1), sex (X_2), the time between surgery and ^{131}I therapy (X_3), the time of THW (X_4), the presence or absence of metastases (lymph node metastasis or lung metastases), (X_5), the presence of absence of Hashimoto's thyroiditis (X_6), serum free triiodothyronine (FT_3) (X_7), free thyroxine (FT_4) (X_8), TSH (X_9), thyroglobulin (Tg) (X_{10}), antithyroglobulin antibody (TgAb) (X_{11}), total cholesterol (TC) (X_{12}), and triglycerides (TG) (X_{13}). Meanwhile, liver function test results including aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total-value bilirubin (TBIL), and direct bilirubin (DBIL) were also collected. Hepatic dysfunction was diagnosed in accordance with the following criteria: the upper limit of normal (ULN) <ALT, AST or GGT<3 times ULN, the ULN<ALP<2 times the ULN and/or TBIL and the ULN<DBIL<2.5 times the ULN were defined as mild hepatic dysfunction; 3 times the ULN <ALT or AST<20 times the ULN, 3 times the ULN< GGT<10 times the ULN, 2 times the ULN<ALP<5 times the ULN and/or 2.5 times the ULN <TBIL, and DBIL<5 time the ULN were defined as moderate hepatic dysfunction; and ALT or AST ≥20 times the ULN, GGT≥10 times the ULN, ALP ≥5 times the ULN and/or TBIL and DBIL≥5 times the ULN were defined as severe hepatic dysfunction[7].

2.4. Parameter assessments

Thyroid function tests were measured by chemiluminescence immunoassays (ADVIA CENTAUR XP SIEMENS AG). Tg and TgAb were detected by the Immulite system

(Immulite 2000 SIEMENS AG). Liver function indices were measured by colorimetry (Hitachi C7600 Japan). TC and TG levels were checked using an auto-analyzer enzymatically (Hitachi Model 7170 analyzer; Hitachi, Ltd., Tokyo, Japan). The dosage range of ^{131}I therapy was 3.7-7.4 GBq.

2.5. Patient follow-up

We measured the serum levels of thyroid parameters, serum lipids, and liver function indices of the 996 patients at 1, 2, 3, and 4 months after ^{131}I therapy to evaluate liver function.

2.6. Statistical analysis

A chi square test was used to analyze differences between ratios. To identify risk factors for hepatic dysfunction, we used a bivariate logistic regression model (univariate analysis) and stepwise logistic regression (multivariate analysis) with a variables with$p< 0.05$, and values <0.05 were considered statistically significant. The odds ratio(OR) was used to evaluate the risk factor. Statistical analysis was performed using SPSS (Statistical Package for Social Sciences) for Windows, version 20 (SPSS, Chicago, IL).

3. Results

3.1. Clinical features of hepatic dysfunction

Overall, 31.6% (315/996) of patients with DTC had hepatic dysfunction. Most patients with hepatic dysfunction had no obvious clinical symptoms except for abnormal liver function indices. The most common abnormality was elevated ALT and (or) AST, with a prevalence of 47.5%. The prevalence rates of mild, moderate, and severe hepatic dysfunction were 80.0% (252/315), 20.0% (63/315), and 0% (0/315), respectively.

3.2. Risk factors for hepatic dysfunction in DTC patients

In this paper, a binary logistic regression model was established for relevant factors of hepatic dysfunction, and single-factor analysis and binary multivariate logistic regression analysis were performed. Patient characteristics were compared using bivariate logistic univariate regression analysis between the 2 groups (Table 1). In the metastase group, the number of patients with hepatic dysfunction and lymph node metastasis or lung metastases were 508 and 21 respectively; and the number of

patients without hepatic dysfunction were 245 (with lymph node metastasis) and 12 (with lung metastases) respectively. The results showed that for male patients, the THW time, FT_3<2.01 pmol/L, FT_4<4.78 pmol/L, TSH >78.195 μIU/mL, TC>5.17 mmol/L, and TG>1.71 mmol/L were closely associated with hepatic dysfunction (odds ratio [OR]: 0.324-3.171, all P<0.01).

Furthermore, we used multivariate logistic regression analysis to screen for relevant factors. In our study, we suggested the following assignments for independent variables: X_1=1 for age≤45 years and X_1=2 for age >45 years; X_2=1 for male sex and X_2=2 for female sex; X_3=1 if the time between total thyroidectomy and ^{131}I therapy was less than 3 months and X_3=2 if the time between total thyroidectomy and ^{131}I therapy was more than 3 months; X_4=1, 2, and 3 if the THW time was shorter than 3 weeks, 3-4 weeks, and longer than 4 weeks, respectively; X_5=1 for the presence of metastases and X_5=2 for the absence of metastases; X_6=1 for the presence of Hashimoto's thyroiditis and X_6=2 for the absence of Hashimoto's thyroiditis; X_7=1, 2, 3, and 4 for FT_3 levels lower than 1.60 pmol/L, 1.60-2.01 pmol/L, 2.01-2.37 pmol/L, and higher than 2.37 pmol/L, respectively; X_8=1, 2, 3, and 4 for FT_4 levels lower than 3.80 pmol/L, 3.80-4.78 pmol/L, 4.78-5.79 pmol/L, and higher than 5.79 pmol/L, respectively; X_9=1, 2, 3, and 4 for TSH levels lower than 57.01 μIU/mL, 57.01-78.20 μIU/mL, 78.20-101.84 μIU/mL, and higher than 101.84 μIU/mL, respectively; X_{10}=1, 2, 3, and 4 for Tg levels lower than 0.50 ng/mL, 0.50-2.64 ng/mL, 2.64-9.18 ng/mL, and higher than 9.18 ng/mL, respectively; X_{11}=1 for TgAb levels lower than 40 IU/mL and X_{11}=2 for TgAb levels higher than 40 IU/mL; X_{12}=1, 2, 3, and 4 for TC levels lower than 5.46 mmol/L, 5.46-6.27 mmol/L, 6.27-7.22 mmol/L, and higher than 6.27 mmol/L, respectively; and X_{13}=1, 2, 3, and 4 for TG levels lower than 1.28 mmol/L, 1.28-1.85 mmol/L, 1.85-2.76 mmol/L, and higher than 2.76 mmol/L, respectively. Resultant variable: Y=1 for patients with hepatic dysfunction, and Y=0 for patients without hepatic dysfunction. Forward stepwise regression analysis rejecting trends ultimately revealed that male sex, FT_4<3.80 pmol/L and TG≥1.28 mmol/L were independent risk factors predicting hepatic dysfunction in patients with DTC (Table 2).

3.3. Outcomes of hepatic dysfunction after ^{131}I therapy

The outcomes of hepatic dysfunction of varying degrees after ^{131}I therapy are displayed in Table 3. The remission rate of patients at 1 month after ^{131}I therapy was 86.34% (272/315). Liver function test results returned to normal in 90.07% (227/252) of patients with mild hepatic dysfunction 1 month after ^{131}I therapy. Moreover, the remission rate among patients with moderate and severe hepatic dysfunction was 71.43% (45/63). Additionally, the remission rate of mild hepatic dysfunction was higher than that of moderate dysfunction (P<0.001).

Remission of hepatic dysfunction at 1 month after ^{131}I therapy is shown in Table 4. The liver function tests of 252 patients with mild hepatic dysfunction were evaluated at 1 month after ^{131}I therapy, the results of which returned to normal in 94.34% (50/53) of patients who were given hepatoprotective treatment [oral bicyclol tablets, Bicyclol 25 mg/tablet, Beijing Union Pharmaceutical Factory, Beijing, China, at a total daily dose of 75mg (25mg three times daily), the treated group]. Moreover, we found that the remission rate among patients in the untreated group was 88.94% (177/199). No remarkable difference in the remission rate was observed between the two groups (P=0.184).

63 patients with moderate hepatic dysfunction were treated with hepatoprotective therapy [oral bicyclol tablets, at a total daily dose of 150mg (50mg three times daily)], and the remission rates among patients at 1 month, 2 months, and 3 months after ^{131}I therapy were 55.6% (35/63), 36.5% (23/63), and 7.9% (5/63) respectively. The time until liver function returned to normal in patients with moderate hepatic dysfunction was 1.8 months.

3.4. The correlation between serum TG and the remission rate of hepatic dysfunction in patients with DTC

A total of 559 patients (218 males, 341females) had elevated serum TG before ^{131}I therapy, including 189 patients with hepatic dysfunction(76 males,113 females). All patients were divided into 2 subgroups based on their serum TG levels 1 month after ^{131}I therapy, subgroup 1: subjects with a normal TG level (141 patients), and subgroup 2: subjects with elevated TG (48 patients). Liver function tests results returned to normal in 92.90% (131/141) of the patients in subgroup 1. Moreover, the remission rate of the patients in subgroup 2 was 75% (36/48) (χ^2=5.382, P=0.02).

4. Discussion

A complex relationship between the thyroid gland and the liver exists in both healthy and disease states[8]. Maliks research showed that thyroid dysfunction may

affect liver function, [9]. A relationship has been suggested to exist between nonalcoholic fatty liver disease (NAFLD) and thyroid dysfunction[10]. Several studies conducted in some countries worldwide showed the relationship between levels of thyroid hormones and the incidence of NAFLD was inverse [11]. In clinical practice, we have found that hepatic dysfunction in DTC patients is common, and most of these patients have no obvious symptoms. The mechanism may be related to the following factors[12]: (1) hypothyroidism may have features similar to those of liver disease (pseudo-liver disease; such as myalgias, fatigue and muscle cramps in the presence of elevated aspartate aminotransferase from myopathy, coma; (2) hypothyroidism may interact liver structure or function directly; in experimental hypothyroidism, with the decrease of the activity of bilirubin UDP-glucuronyltransferase, bilirubin excretion is reduced; (3) hypothyroidism is related to cholestatic jaundice due to decreased bilirubin and bile excretion[13]; and (4) severe hypothyroidism is known to cause increased permeability of the vascular endothelium[14].

Our study demonstrated that 31.6% of DTC patients suffered from different degrees of hepatic dysfunction. All of these patients had mild or moderate liver injury. Additionally, an increase in ALT or AST was the most common abnormal indicator, and the prevalence was 47.5%. The findings are different from previous research data from Gokmen's group whose research showed that hypertriglyceridemia and a higher FT_3/FT_4 ratio are independent risk factors for NAFLD, however, hypothyroidism is not related to the condition directly [15]. However, their research subjects were patients with hypothyroidism, where hypothyroidism was defined only by a TSH level $\geq$ 4.1 mIU/L, and FT_3 and FT_4 levels were not included. The FT_3 and FT_4 levels of some patients were normal.

To explore the risk factors of hepatic dysfunction for DTC patients, we analyzed 13 related factors, such as age and sex, and found that male sex, a THW time greater than 21 days, FT_3<2.01 pmol/L, FT_4<4.78 pmol/L, TSH>78.195 μIU/mL, TC>5.17 mmol/L, and TG>1.71 mmol/L were risk factors for hepatic dysfunction in the univariate analysis (all P<0.01). Additionally, we found that male sex, FT_4<3.80 pmol/L and TG≥1.28 mmol/L were more closely associated with hepatic dysfunction in DTC patients in the multivariate logistic regression analysis (P<0.01). No studies related to our study on the risk factors of hepatic dysfunction for DTC patients were found.

In this study, we found that the remission rate of patients with mild hepatic dysfunction was significantly higher than that of patients with moderate hepatic dysfunction at 1 month after ^{131}I therapy. Additionally, the remission rate among patients with mild hepatic dysfunction was not significantly different between the treated group and the untreated group. We also found that the FT_4 level is associated with hepatic dysfunction, with more severe hypothyroidism corresponding to a greater impact on liver function. Patients with mild hepatic dysfunction may not be treated with hepatoprotective drugs because the remission rate of hepatic dysfunction at 1 month after ^{131}I therapy was not significantly different between the treated group and the untreated group. Recent studies revealed that with no liver damage, hepatic dysfunction associated with hypothyroidism can be reversed over several weeks with

thyroxine replacement [16].

Additionally, liver is the vital organ for cholesterol metabolism, thyroid hormones play an important role in hepatic lipid metabolism[17]. Thyroid hormones increase the activity of lipid-lowering liver enzymes which can lead to a reduction in low-density lipoprotein levels [18]. Serum lipids also play an important role in liver function[19], which coincided with the results of our study. In our study, hepatic function indices returned to normal at 1 month after ^{131}I therapy in 86.34% of the patients, the remission rate in patients with normal TG levels was significantly higher than that in the elevated TG group, and the time until liver dysfunction returned to normal in the patients suffering from hyperlipidemia and hepatic dysfunction was longer than that in the patients suffering from only hyperlipidemia. In other words, lipid-lowering therapy(statins or fenofibrate) was very important for patients with hepatic dysfunction.

Obesity is a important metabolic risk factor of liver and thyroid dysfunction, and it would be helpful if we analysis of the influence of it in our study. For these reasons, further rigorous prospective studies are needed to confirm these preliminary findings.

Conclusions

Hepatic dysfunction is more likely to occur in male patients and patients with a THW time greater than 21 days, FT_3<2.01 pmol/L, FT_4<4.78 pmol/L, TSH>78.195 μIU/mL, TC>5.17 mmol/L, and TG>1.71 mmol/L. Additionally, lipid-lowering therapy is particularly important for DTC patients with hepatic dysfunction before ^{131}I therapy. For DTC patients with hepatic dysfunction combined with dyslipidemia, lipid-lowering therapy is recommended, which is expected to shorten the remission time of hepatic dysfunction.

Contribution to the Field Statement: An elevated TSH level is essential to stimulate ^{131}I uptake when patient with DTC undergoes RAI therapy. A number of patients suffer from general edema, constipation and so on, before RAI therapy with THW. Evidence reveals that hypothyroidism may have a direct effect on liver structure or function. We retrospectively collected clinical data from 996 patients with DTC to investigate risk factors of hepatic dysfunction in these patients. Patients with mild hepatic dysfunction and ortholiposis were found to have a higher likelihood of recovering normal liver function. For males, FT_4 and TG levels were more closely related to hepatic dysfunction, and the prognosis of hepatic dysfunction was closely associated with the level of TG.

Contributorship Statement： Yanhui Ji and Renfei Wang contributed to the conception and design of the study. Yanhui Ji, Wei Zheng, Jian Tan, and Cailan Wu assisted with data acquisition. Yanhui Ji , Zhaowei Meng, and Renfei Wang conducted the statistical analyses and drafted the manuscript. Jian Tan, Zhaowei Meng critically revised the manuscript. All authors read and approved the final manuscript and agree to be accountable for all aspects of the research in ensuring that the accuracy or integrity of any part of the work are appropriately investigated and resolved.**Competing interests**

There are no competing interests for any author

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Data sharing statement

All data relevant to the study included in the article are uploaded as supplementary information

Ethical Approval statement

The studies involving human participants were reviewed and approved by Ethical Committee of Tianjin Medical University General Hospital (NO. IRB2020-WZ-001). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

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Table 1 Bivariate logistic univariate regression of the factors for DTC patients with hepatic dysfunction

Relevant factors		With hepatic dysfunction (n[%])	Without hepatic dysfunction (n[%])	B value	OR value	95%CI	P
Age	≤45	350(68.50%)	161(31.50%)	-1.011	1	0.744-1.321	0.934
	>45	331(68.25%)	154(31.75%)		1.011		
Sex	Male	158(50.97%)	152(49.03%)	-1.127	1	0.244-0.430	0.000

	Female	523(76.24%)	163(23.76%)		0.324		
the time between	≤3 months	560(68.20%)	261(31.80%)	0.043	1	0.734-1.486	0.810
thyroidectomy and ^{131}I	>3 months	121(69.14%)	54(30.86%)		1.044		
therapy							
Thyroid hormone	≤21 days	372(72.51%)	141(27.49%)	0.396	1	0.517-0.892	0.005
withdrawal time	>21 days	309(63.98%)	174(36.02%)		1.486		
Metastases	Negative	152(72.38%)	58(27.62%)	-0.242	1	0.561-1.100	0.160
	Positive	529(67.30%)	257(32.70%)		0.785		
Hashimoto's thyroiditis	Negative	595(67.85%)	282(32.15%)	-0.211	1	0.529-1.239	0.331
	Positive	86(72.27%)	33(27.73%)		0.810		
FT_3	<2.01*	316(63.71%)	180(36.29%)	0.432	1	1.177-2.016	0.002
	≥2.01	365(73.00%)	135(27.00%)		1.540		
FT_4	<4.78*	280(56.34%)	217(43.66%)	1.154	1	2.389-4.209	0.000
	≥4.78	401(80.36%)	98(19.64%)		3.171		
TSH	<78.195*	365(73.29%)	133(26.71%)	-0.458	1	0.483-0．828	0.001
	≥78.195	316(63.45%)	182(36.55%)		0.633		
Tg	<2.635*	346(69.48%)	152(30.52%)	-0.185	1	0.609-1.134	0.244
	≥2.635	335(67.27%)	163(32.73%)		0.831		
TgAb	≤40△	527(66.96%)	260(33.04%)	0.381	1	0.979-1.930	0.067
	>40	154(73.68%)	55(26.32%)		1.374		
TC	≤5.17△	129(75.44%)	42(24.56%)	0.758	1	1.615-2.822	0.000
	>5.17	552(66.90%)	273(33.10%)		2.135		
TG	≤1.71△	336(77.42%)	98(22.58%)	-0.418	1	0.451-0.960	0.03
	>1.71	344(61.54%)	215(38.46%)		0.658		

373 CI=confidence interval, OR=odds ratio, *median; △Upper limit of the normal value

374 Table 2 Bivariate logistic multivariate regression analysis of the factors for DTC patients with hepatic

375 dysfunction

Causal variable	B	Standard error	Wald	df	P	EXP (B)	95%CI
X_2	-0.933	0.156	35.703	1	0.000	0.393	0.290-0.534
X_8 (FT_4)			62.291	3	0.000		
X_8 (2)	-0.347	0.193	3.249	1	0.071	0.707	0.485-1.031
X_8 (3)	-0.853	0.200	18.146	1	0.000	0.426	0.288-0.631
X_8 (4)	-1.789	0.239	55.817	1	0.000	0.167	0.105-0.267
X_{13}			15.195	3	0.002		

X_{13} (2)	0.325	0.225	2.072	1	0.150	1.383	0.889-2.152
X_{13} (3)	0.643	0.223	8.313	1	0.004	1.901	1.228-2.943
X_{13} (4)	0.787	0.219	12.784	1	0.000	2.197	1.429-3.376
Constant	-0.188	0.270	0.484	1	0.487	0.829	

Table 3 Outcomes of hepatic dysfunction of varying degrees after 1 month of ^{131}I therapy

Degree	n	Outcomes (n[%])	
		Remission	Nonremission
Mild	252	227 (90.07%)	25 (9.93%)
Moderate	63	45 (71.43%)	18 (28.57%)
χ^2		14.873	
p		0.000	

Table 4 Remission of hepatic dysfunction among patients given different treatments at 1 month after ^{131}I therapy

Group	n	Outcomes (n[%])	
		Remission	Nonremission
Treatment	53	50 (94.34%)	3 (5.66%)
No treatment	199	177 (88.94%)	22 (11.06%)
χ^2		1.765	
p		0.184	

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract "Influence of Hypothyroidism on Liver Function Before Radioiodine Therapy " in title indicated the study's design
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found The purpose "The present study aimed to investigate the risk factors for hepatic dysfunction before radioiodine (RAI) therapy in patients with differentiated thyroid cancer (DTC)." In line 19-21,on page 1 of revised manuscript(main document) provide what was done; "Patients with minor hepatic dysfunction and ortholiposis are more likely to recover normal liver function. Patients with moderate hepatic dysfunction should be treated with hepatoprotective drugs. For males, FT_4 and TG levels tended to be associated with hepatic dysfunction, and the prognosis of hepatic dysfunction was closely related to the level of TG." in Line 36-40 on page 2 of revised manuscript(main document) provide what was we found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported "When DTC patient undergoes RAI therapy, an elevated thyroid-stimulating hormone (thyrotropin, TSH) level is essential, Evidence indicates that hypothyroidism may affect liver function or structure directly. Therefore, identification of factors resulting in hepatic dysfunction is crucial" is line63-68 on page 2 of revised manuscript(main document)
Objectives	3	State specific objectives, including any prespecified hypotheses The objective is "to investigate risk factors for patients with hepatic dysfunction using a retrospective approach" in line 68-69 on page 2 of revised manuscript(main document)
Methods		
Study design	4	Present key elements of study design early in the paper The key elements of study design is how to determine the "Participants or Criteria selection", it was showed in line 77-86 on page 3 of revised manuscript(main document)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection It was showed in line 88-107 on page 3 and 116-118 on page 4 of revised manuscript(main document)
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants

		It was showed in line 77-107 on page 3 of revised manuscript(main document)
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable It was showed in 129-203 on page 3-4 of revised manuscript(main document)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group It was showed in 109-114on page 3-4 of revised manuscript(main document)
Bias	9	Describe any efforts to address potential sources of bias It was showed in 264-266 on page 8 of revised manuscript(main document)
Study size	10	Explain how the study size was arrived at It was showed in 77-80 on page 3of revised manuscript(main document)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why It was showed in 88-107 on page 3of revised manuscript(main document)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses It was showed in 120-126 on page 4 of revised manuscript(main document)

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time It was showed in 128-203 on page4-6 of revised manuscript(main document)
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives In line 231-239 on page 7 of revised manuscript(main document)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias In line 41-51 on page 2 and in line 264-266 on page 8 of revised manuscript(main document)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence in line 221-263 on page 7 and 8 of revised manuscript(main document)
Generalisability	21	Discuss the generalisability (external validity) of the study results in line 275-284 on page 8 of revised manuscript(main document)
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

This study was sponsored by the Natural Science Foundation of Tianjin City(Grant No.20JCQNJC01610) in line 295-296 on page 9 of revised manuscript(main document)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely

available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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A Retrospective Study of The Influence of Hypothyroidism on Liver Function Before Radioiodine Therapy in China: A Comparison Analysis based on Patients with Differentiated Thyroid Cancer

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Title page:

A Retrospective Study of The Influence of Hypothyroidism on Liver Function Before Radioiodine Therapy in China: A Comparison Analysis based on Patients with Differentiated Thyroid Cancer

Running title: The Influence of hypothyroidism on the Liver Function in Patients with Differentiated Thyroid Cancer

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Abstract

Purpose The aim of present study is to investigate the risk factors for hepatic dysfunction before radioiodine (RAI) therapy in patients with differentiated thyroid cancer (DTC). ***Methods*** 996 patients (314 males, 682 females; ageof 45.07±12.98 years) with postoperative of DTC were recruited and divided into two groups including patients with and without hepatic dysfunction. The changes in baseline data and traced liver function levels together with other metabolic profiles were compared between the two groups. ***Result*** Overall, 31.6% of patients had hepatic dysfunction. Higher aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) was the most common abnormality (the prevalence rate was 47.5%). The percentages of mild and moderate hepatic dysfunction were 80.0% and 20.0%, respectively. Univariate analyses demonstrated that the most prominent risk factors for hepatic dysfunction (odds ratio [OR]=0.324-3.171, P<0.01) were male sex

with levothyroxine discontinuation and free triiodothyronine (FT_3)< 2.01 pmol/L, free thyroxine (FT_4)<4.78 pmol/L, thyroid-stimulating hormone (TSH)>78.195 μIU/mL, total cholesterol (TC)>5.17 mmol/L , triglycerides (TG)>1.71 mmol/L and more than 21 days of thyroid hormone withdrawal (THW) . Multivariate analyses demonstrated that for males, FT_4<3.80 pmol/L and TG≥1.28 mmol/L were the most prominent risk factors.. ***Conclusions*** Patients with minor hepatic dysfunction and ortholiposis are more likely to recover to normal liver function. Patients with moderate hepatic dysfunction should be treated with hepatoprotective drugs. For males, FT_4 and TG levels tended to be associated with hepatic dysfunction, and the prognosis of hepatic dysfunction was closely related to the level of TG.

Strengths and limitations of this study:

Strengths: The results of this study may help nuclear physicians to make clinical treatment strategies of DTC patients.

Limitations: 1. We selected cases with complete data to perform our retrospective analysis,however, the exclusion of a few patients who were lost to follow-up might result in potential bias.

2.We could not collect the result of LDL cholesterol measurements.

3.Obesity is an important metabolic risk factorof liver and thyroid dysfunction, and it would be helpful if we could perform analysis of the influence of it in our study.

For these reasons, further rigorous prospective studies are needed to confirm these preliminary findings.

Keywords: thyroid cancer, ^{131}I, high-dose radioiodine therapy, hepatic dysfunction, risk factors

1. Introduction

Radioiodine (RAI) therapy is a very important procedure to ablate normal thyroid remnant tissues and microscopic deposits of differentiated thyroid carcinoma (DTC) after thyroidectomy [1]. As reported, RAI therapy was able to reduce the number of locoregional recurrences and to increase overall survival of the American Thyroid Association(ATA) intermediate-risk and high risk DTC patients [2 3]. In order to stimulate ^{131}I uptake into the normal thyroid remnants and metastatic tissues of thyroid carcinoma for DTC patients undergo RAI therapy, an elevated thyroid-stimulating hormone (thyrotropin, TSH) level is essential [4]. The classic method of preparation for RAI therapy is thyroid hormone withdrawal (THW). However, the application of THWusually results in some physical or psychological side effects associated with hypothyroidism[5], such as general edema, constipation, and depression. Evidences indicate that hypothyroidism may affect liver function or structure directly [6]. Therefore, the identification of factors that may causing hepatic dysfunction is rather crucial. In the present study, we collected clinical data from 996 patients with DTC to investigate the risk factors for patients with hepatic dysfunction

undergoing a retrospective approach.

2. Materials and methods

2.1. Ethics statement

This study is a retrospective clinical study summarizing and analyzing a large amount of clinical data. The ethics committee of Tianjin Medical University General Hospital waived the need to obtain written informed consent from all patients. All clinical data used in this study were analyzed anonymously.

2.2. Participants or Criteria selection

The study included 996 patients (314 males, 682 females; age of 45.07±12.98 years) who had undergone RAI therapy at our department from January 2012 to March 2018. The patients had undergone complete or partial thyroidectomy performed by various surgeons. The patients agreed to receive RAI therapy and were informed about the traditional preparation method, THW. We used hepatitis virus markers, abdominal ultrasonography, echocardiography, and autoantibody and immunoglobulin subtype determination for patients with hepatic dysfunction to exclude other apparent causes of liver damage. Other possible causes included viral hepatitis, liver cirrhosis or biliary tract disease, chronic cardiac dysfunction and autoimmune liver disease, liver steatosis and hyperlipoidemia, etc[7].

2.3. Patient and Public Involvement statement

This was an uncontrolled retrospective study, patients of this study had underg one RAI therapy at our department, and we recorded and analyzed the data in order to investigate the risk factors for patients with hepatic dysfunction.

2.4. Data collection and grouping All RAI therapy regimens were conducted b y the same nuclear medicine department following a standard protocol (2015 A merican Thyroid Association Management Guidelines). Relevant data were recor ded during the RAI therapy, including patient age (named X_1), sex (X_2), the ti me between surgery and ^{131}I therapy (X_3), the time of THW (X_4), the presence or absence of metastases (lymph node metastasis or lung metastases), (X_5), the p resence of absence of Hashimoto's thyroiditis (X_6), serum free triiodothyronine (FT_3) (X_7), free thyroxine (FT_4) (X_8), TSH (X_9), thyroglobulin (Tg) (X_{10}), antit hyroglobulin antibody (TgAb) (X_{11}), total cholesterol (TC) (X_{12}), and triglycerid es (TG) (X_{13}). Meanwhile, liver function test results including aspartate aminotr ansferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), g amma-glutamyl transferase (GGT), total-value bilirubin (TBIL), and direct biliru

bin (DBIL) were also collected. Hepatic dysfunction was diagnosed in accordance with the following criteria: the upper limit of normal (ULN) <ALT, AST or GGT<3 times ULN, the ULN<ALP<2 times the ULN and/or TBIL and the ULN<DBIL<2.5 times the ULN were defined as mild hepatic dysfunction; 3 times the ULN <ALT or AST<20 times the ULN, 3 times the ULN< GGT<10 times the ULN, 2 times the ULN<ALP<5 times the ULN and/or 2.5 times the ULN <TBIL, and DBIL<5 time the ULN were defined as moderate hepatic dysfunction; and ALT or AST ≥20 times the ULN, GGT≥10 times the ULN, ALP ≥5 times the ULN and/or TBIL and DBIL≥5 times the ULN were defined as severe hepatic dysfunction[7].

2. 5. Parameter assessments

Thyroid function tests were measured by chemiluminescence immunoassays (ADVIA CENTAUR XP SIEMENS AG). Tg and TgAb were detected by the Immulite system (Immulite 2000 SIEMENS AG). Liver function indices were measured by colorimetry (Hitachi C7600 Japan). TC and TG levels were checked using an auto-analyzer enzymatically (Hitachi Model 7170 analyzer; Hitachi, Ltd., Tokyo, Japan). The dosage range of ^{131}I therapy was 3.7-7.4 GBq.

2.6. Patient follow-up

We measured the serum levels of thyroid parameters, serum lipids, and liver function indices of the 996 patients at 1, 2, 3, and 4 months after ^{131}I therapy to evaluate their liver function.

2.7. Statistical analysis

A chi square test was used to analyze the differences between ratios. To identify risk factors for hepatic dysfunction, we used a bivariate logistic regression model (univariate analysis) and stepwise logistic regression (multivariate analysis) with a variablewith $p< 0.05$, and values <0.05 were considered statistically significant. The odds ratio (OR) was used to evaluate the risk factor. Statistical analysis was performed using SPSS (Statistical Package for Social Sciences) for Windows, version 20 (SPSS, Chicago, IL).

3. Results

3.1. Clinical features of hepatic dysfunction

Overall, 31.6% (315/996) of patients with DTC had hepatic dysfunction. Most patients with hepatic dysfunction had no obvious clinical symptoms except for

abnormal liver function indices. The most common abnormality was elevated ALT and (or) AST, with a prevalence of 47.5%. The prevalence rates of mild, moderate, and severe hepatic dysfunction were 80.0% (252/315), 20.0% (63/315), and 0% (0/315), respectively.

3.2. Risk factors for hepatic dysfunction in DTC patients

In this paper, a binary logistic regression model was established for relevant factors of hepatic dysfunction. Single-factor analysis and binary multivariate logistic regression analysis were performed as well. Patient characteristics were compared using bivariate logistic univariate regression analysis between the 2 groups (Table 1). In the metastase group, the number of patients with hepatic dysfunction and lymph node metastasis or lung metastases were 508 and 21 respectively; and the number of patients without hepatic dysfunction were 245 (with lymph node metastasis) and 12 (with lung metastases) respectively. The results showed that for male patients, the THW time, FT_3<2.01 pmol/L, FT_4<4.78 pmol/L, TSH >78.195 μIU/mL, TC>5.17 mmol/L, and TG>1.71 mmol/L were closely associated with hepatic dysfunction (odds ratio [OR]: 0.324-3.171, all P<0.01).

Furthermore, the multivariate logistic regression analysis were applied to screen the relevant risk factors. In our study, we suggested the following assignments for independent variables: X_1=1 for age≤45 years and X_1=2 for age >45 years; X_2=1 for male sex and X_2=2 for female sex; X_3=1 if the time between total thyroidectomy and ^{131}I therapy was less than 3 months and X_3=2 if the time between total thyroidectomy and ^{131}I therapy was more than 3 months; X_4=1, 2, and 3 if the THW time was shorter than 3 weeks, 3-4 weeks, and longer than 4 weeks, respectively; X_5=1 for the presence of metastases and X_5=2 for the absence of metastases; X_6=1 for the presence of Hashimoto's thyroiditis and X_6=2 for the absence of Hashimoto's thyroiditis; X_7=1, 2, 3, and 4 for FT_3 levels lower than 1.60 pmol/L, 1.60-2.01 pmol/L, 2.01-2.37 pmol/L, and higher than 2.37 pmol/L, respectively; X_8=1, 2, 3, and 4 for FT_4 levels lower than 3.80 pmol/L, 3.80-4.78 pmol/L, 4.78-5.79 pmol/L, and higher than 5.79 pmol/L, respectively; X_9=1, 2, 3, and 4 for TSH levels lower than 57.01 μIU/mL, 57.01-78.20 μIU/mL, 78.20-101.84 μIU/mL, and higher than 101.84 μIU/mL,

respectively; X_{10}=1, 2, 3, and 4 for Tg levels lower than 0.50 ng/mL, 0.50-2.64 ng/mL, 2.64-9.18 ng/mL, and higher than 9.18 ng/mL, respectively; X_{11}=1 for TgAb levels lower than 40 IU/mL and X_{11}=2 for TgAb levels higher than 40 IU/mL; X_{12}=1, 2, 3, and 4 for TC levels lower than 5.46 mmol/L, 5.46-6.27 mmol/L, 6.27-7.22 mmol/L, and higher than 6.27 mmol/L, respectively; and X_{13}=1, 2, 3, and 4 for TG levels lower than 1.28 mmol/L, 1.28-1.85 mmol/L, 1.85-2.76 mmol/L, and higher than 2.76 mmol/L, respectively. Resultant variable: Y=1 for patients with hepatic dysfunction, and Y=0 for patients without hepatic dysfunction. Forward stepwise regression analysis rejecting trends ultimately revealed that male sex, FT_4<3.80 pmol/L and TG≥1.28 mmol/L were independent risk factors to predict hepatic dysfunction in patients with DTC (Table 2).

3.3. Outcomes of hepatic dysfunction after ^{131}I therapy

The outcomes of hepatic dysfunction of varying degrees after ^{131}I therapy are displayed in Table 3. The remission rate of patients at 1 month after ^{131}I therapy was 86.34% (272/315). Liver function test results revealed that 90.07% (227/252) of patients with mild hepatic dysfunction returned to normal 1 month after ^{131}I therapy. Moreover, the remission rate among patients with moderate and severe hepatic dysfunction was 71.43% (45/63). Additionally, the remission rate of mild hepatic dysfunction was higher than that of moderate dysfunction (P<0.001).

The remission of hepatic dysfunction at 1 month after ^{131}I therapy is shown in Table 4. The liver function tests of 252 patients with mild hepatic dysfunction were evaluated at 1 month after ^{131}I therapy, Results showed that the liver function of 94.34% (50/53) of patients who were given hepatoprotective treatment [oral bicyclol tablets, Bicyclol 25 mg/tablet, Beijing Union Pharmaceutical Factory, Beijing, China, at a total daily dose of 75mg (25mg three times daily), the treated group] returned to normal after 1 month after ^{131}I therapy. Moreover, the remission rate among patients in the untreated group was found to be 88.94% (177/199). However no remarkable difference in the remission rate was observed between the two groups (P=0.184).

Other 63 patients with moderate hepatic dysfunction were treated with hepatoprotective therapy [oral bicyclol tablets, at a total daily dose of 150mg (50mg three times daily)], and the remission rates among patients at 1 month, 2 months, and

3 months after ^{131}I therapy were 55.56% (35/63), 36.5% (23/63), and 7.94% (5/63) respectively. The aveage time for liver function returned to normal level in patients with moderate hepatic dysfunction was 1.8 months.

3.4. The correlation between serum TG and the remission rate of hepatic dysfunction in patients with DTC

The number of patients with hyperlipidemia , hyperlipidemia with hepatic dysfunction, and dyslipidemia (hypercholesterolemia + hypertriglyceridemia) were 564, 278 and 244 respectively. A total of 559 patients (218 males, 341femails) had elevated serum TG before ^{131}I therapy, including 189 patients with hepatic dysfunction (76 males, 113 females). All patients were divided into 2 subgroups based on their serum TG levels 1 month after ^{131}I therapy subgroup 1 includes subjects with a normal TG level (141 patients) and subgroup 2 includes subjects with elevated TG (48 patients, 21 femails, 27mails). In subgroup 2, 15 males and 10 femails were treated with statins or fenofibrate for lipid-lowering therapy . The percentage of patients with liver function returned to normal was 92.90% (131/141) in subgroup 1. Moreover, the remission rate of the patients in subgroup 2 was 75.00% (36/48) (χ^2=5.382, P=0.02). In subgroup 2, the remission rate of the patients with lipid-lowering therapy was 84.00%(21/25) and 65.21%(15 /23).

4. Discussion

A complex relationship between the thyroid gland and the liver exists in both healthy and disease states[8]. Maliks research showed that thyroid dysfunction may affect liver function [9]. It is suggested that a relationship may exists between nonalcoholic fatty liver disease (NAFLD) and thyroid dysfunction[10]. Several studies conducted in some countries worldwide showed that the relationship between levels of thyroid hormones and the incidence of NAFLD was inverse [11]. In clinical practice, we have found that hepatic dysfunction in DTC patients is common, and most of these patients have no obvious symptoms. The mechanism may be related to the following factors[12]: (1) hypothyroidism may have features similar to those of liver diseases (pseudo-liver disease; such as myalgias, fatigue and muscle cramps in the presence of elevated aspartate aminotransferase from myopathy, coma); (2) hypothyroidism may

interact with liver structure or function directly,for example, bilirubin excretion is reduced in experimental hypothyroidism with the decrease of the activity of bilirubin UDP-glucuronyltransferase; (3) hypothyroidism is related to cholestatic jaundice due to decreased bilirubin and bile excretion[13]; and (4) severe hypothyroidism is known to cause increased permeability of the vascular endothelium[14].

Our study demonstrated that 31.6% of DTC patients suffered from different degrees of hepatic dysfunction. All of these patients had mild or moderate liver injury. Additionally, an increase in ALT or AST was the most common abnormal indicator, and the prevalence was 47.5%. The findings are different from previous research data from Gokmen's group whose research showed that hypertriglyceridemia and a higher FT_3/FT_4 ratio are independent risk factors for NAFLD, however, hypothyroidism is not related to the condition directly [15]. However, their research subjects were patients with hypothyroidism, where hypothyroidism was defined only by a TSH level $\geq$ 4.1 mIU/L, and FT_3 and FT_4 levels were not included. The FT_3 and FT_4 levels of some patients were normal.

To explore the risk factors of hepatic dysfunction for DTC patients, we analyzed 13 related factors, and found that male sex, a THW time greater than 21 days, FT_3<2.01 pmol/L, FT_4<4.78 pmol/L, TSH>78.195 μIU/mL, TC>5.17 mmol/L, and TG>1.71 mmol/L were responsible risk factors for hepatic dysfunction in the univariate analysis (all P<0.01). Additionally, we found that male sex, FT_4<3.80 pmol/L and TG≥1.28 mmol/L were closely associated with hepatic dysfunction in DTC patients in the multivariate logistic regression analysis (P<0.01). No other studies related to our study on the risk factors of hepatic dysfunction for DTC patients were found.

In this study, we found that the remission rate of patients with mild hepatic dysfunction was significantly higher than that of patients with moderate hepatic dysfunction at 1 month after ^{131}I therapy. Additionally, no significant differences can be found on the remission rate among patients with mild hepatic dysfunction between the treated and untreated groups. It was also found that the FT_4 level is highly associated with hepatic dysfunction, with more severe hypothyroidism corresponding

to a greater impact on liver function. Patients with mild hepatic dysfunction may not be treated with hepatoprotective drugs because the remission rate of hepatic dysfunction at 1 month after ^{131}I therapy was not significantly different between the treated and untreated groups. Recent studies revealed that with no liver damage, hepatic dysfunction associated with hypothyroidism can be reversed over several weeks with thyroxine replacement [16].

Additionally, liver is the vital organ for cholesterol metabolism and thyroid hormones, which plays an important role in hepatic lipid metabolism[17]. Thyroid hormones can increase the activity of lipid-lowering liver enzymes which can cause a reduction in low-density lipoprotein levels [18]. As reported, serum lipids also play an important role in liver function[19] , which coincided with the results of our study. In our study, hepatic function indices returned to normal at 1 month after ^{131}I therapy in 86.34% of the patients, the remission rate in patients with normal TG levels was significantly higher than that in the elevated TG group. In addition, the time until liver dysfunction returned to normal level in the patients suffering from hyperlipidemia and hepatic dysfunction was longer than that of the patients suffering from onlyhepatic dysfunction . In other words, lipid-lowering therapy (statins or fenofibrate) was very important for patients with hepatic dysfunction.

Obesity is an important metabolic risk factor of liver and thyroid dysfunction, and it would be helpful if we could analysis of the influence of it in our study. However, due to the limitations, this part of analysis was not included in the current paper. For this reason, further rigorous prospective studies are needed to confirm these preliminary findings.

Conclusions

Hepatic dysfunction is more likely to occur in male patients and patients with a THW time greater than 21 days, FT_3<2.01 pmol/L, FT_4<4.78 pmol/L, TSH>78.195 μIU/mL, TC>5.17 mmol/L, and TG>1.71 mmol/L. Additionally, lipid-lowering therapy is particularly important for DTC patients with hepatic dysfunction before ^{131}I therapy. For DTC patients with hepatic dysfunction combined with dyslipidemia, lipid-lowering therapy is recommended, which is expected to shorten the remission

time of hepatic dysfunction.

Contribution to the Field Statement: An elevated TSH level is essential to stimulate ^{131}I uptake when patient with DTC undergoes RAI therapy. A number of patients suffer from general edema, constipation and so on, before RAI therapy with THW. Evidence reveals that hypothyroidism may have a direct effect on liver structure or function. We retrospectively collected clinical data from 996 patients with DTC to investigate the relevant risk factors of hepatic dysfunction in these patients. Patients with mild hepatic dysfunction and ortholiposis were found to have a higher likelihood of recovering to normal liver function. For males, FT_4 and TG levels were more closely related to hepatic dysfunction, and the prognosis of hepatic dysfunction was closely associated with the level of TG.

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Competing interests

There are no competing interests for any author

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Data sharing statement

All data relevant to the study included in the article are uploaded as supplementary information**Ethical Approval statement**

The studies involving human participants were reviewed and approved by Ethical Committee of Tianjin Medical University General Hospital (NO. IRB2020-WZ-001). Written informed consent to participate in this study was provided by the participants'

legal guardian/next of kin.

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Table 1 Bivariate logistic univariate regression of the factors for DTC patients with hepatic dysfunction

Relevant factors		With hepatic dysfunction (n[%])	Without hepatic dysfunction (n[%])	B value	OR value	95%CI	P
Age	≤45	350(68.50%)	161(31.50%)	-1.011	1	0.744-1.321	0.934
	>45	331(68.25%)	154(31.75%)		1.011		
Sex	Male	158(50.97%)	152(49.03%)	-1.127	1	0.244-0.430	0.000
	Female	523(76.24%)	163(23.76%)		0.324		
the time between thyroidectomy and ^{131}I therapy	≤3 months	560(68.20%)	261(31.80%)	0.043	1	0.734-1.486	0.810
	>3 months	121(69.14%)	54(30.86%)		1.044		
Thyroid hormone withdrawal time	≤21 days	372(72.51%)	141(27.49%)	0.396	1	0.517-0.892	0.005
	>21 days	309(63.98%)	174(36.02%)		1.486		
Metastases	Negative	152(72.38%)	58(27.62%)	-0.242	1	0.561-1.100	0.160
	Positive	529(67.30%)	257(32.70%)		0.785		
Hashimoto's thyroiditis	Negative	595(67.85%)	282(32.15%)	-0.211	1	0.529-1.239	0.331
	Positive	86(72.27%)	33(27.73%)		0.810		

FT_3	<2.01*	316(63.71%)	180(36.29%)	0.432	1	1.177-2.016	0.002
	≥2.01	365(73.00%)	135(27.00%)		1.540		
FT_4	<4.78*	280(56.34%)	217(43.66%)	1.154	1	2.389-4.209	0.000
	≥4.78	401(80.36%)	98(19.64%)		3.171		
TSH	<78.195*	365(73.29%)	133(26.71%)	-0.458	1	0.483-0．828	0.001
	≥78.195	316(63.45%)	182(36.55%)		0.633		
Tg	<2.635*	346(69.48%)	152(30.52%)	-0.185	1	0.609-1.134	0.244
	≥2.635	335(67.27%)	163(32.73%)		0.831		
TgAb	≤40△	527(66.96%)	260(33.04%)	0.381	1	0.979-1.930	0.067
	>40	154(73.68%)	55(26.32%)		1.374		
TC	≤5.17△	129(75.44%)	42(24.56%)	0.758	1	1.615-2.822	0.000
	>5.17	552(66.90%)	273(33.10%)		2.135		
TG	≤1.71△	336(77.42%)	98(22.58%)	-0.418	1	0.451-0.960	0.03
	>1.71	344(61.54%)	215(38.46%)		0.658		

384 CI=confidence interval, OR=odds ratio, *median; △Upper limit of the normal value

385 Table 2 Bivariate logistic multivariate regression analysis of the factors for DTC patients with hepatic

386 dysfunction

Causal variable	B	Standard error	Wald	df	P	EXP (B)	95%CI
X_2	-0.933	0.156	35.703	1	0.000	0.393	0.290-0.534
X_8 (FT_4)			62.291	3	0.000		
X_8 (2)	-0.347	0.193	3.249	1	0.071	0.707	0.485-1.031
X_8 (3)	-0.853	0.200	18.146	1	0.000	0.426	0.288-0.631
X_8 (4)	-1.789	0.239	55.817	1	0.000	0.167	0.105-0.267
X_{13}			15.195	3	0.002		
X_{13} (2)	0.325	0.225	2.072	1	0.150	1.383	0.889-2.152
X_{13} (3)	0.643	0.223	8.313	1	0.004	1.901	1.228-2.943
X_{13} (4)	0.787	0.219	12.784	1	0.000	2.197	1.429-3.376
Constant	-0.188	0.270	0.484	1	0.487	0.829	

387

388 Table 3 Outcomes of hepatic dysfunction of varying degrees after 1 month of ^{131}I therapy

Degree	n	Outcomes (n[%])	
		Remission	Nonremission
Mild	252	227 (90.07%)	25 (9.93%)

Moderate	63	45 (71.43%)	18 (28.57%)
χ^2		14.873	
p		0.000	

Table 4 Remission of hepatic dysfunction among patients given different treatments at 1 month after ^{131}I therapy

Group	n	Outcomes (n[%])	
		Remission	Nonremission
Treatment	53	50 (94.34%)	3 (5.66%)
No treatment	199	177 (88.94%)	22 (11.06%)
χ^2		1.765	
p		0.184	