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 aim of the present study is to investigate the risk factors for hepatic dysfunction before radioiodine therapy in patients with differentiated thyroid cancer (DTC).

Methods 996 patients (314 men, 682 women; age of 45.07±12.98 years) with postoperative 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 and/or alanine aminotransferase 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 (OR=0.324–3.171, p<0.01) were male sex with levothyroxine discontinuation and free triiodothyronine <2.01 pmol/L, free thyroxine (FT4) <4.78 pmol/L, thyroid-stimulating hormone >78.195 µIU/mL, total cholesterol >5.17 mmol/L, triglycerides (TG) >1.71 mmol/L and more than 21 days of thyroid hormone withdrawal. Multivariate analyses demonstrated that for men, FT4 <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 men, FT4 and TG levels tended to be associated with hepatic dysfunction, and the prognosis of hepatic dysfunction was closely related to the TG level.

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. 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 patients with DTC. In order to stimulate ¹³¹I uptake into the normal thyroid remnants and metastatic tissues of thyroid carcinoma for patients with DTC who have undergone RAI therapy, an elevated thyroid-stimulating hormone (thyrotropin, TSH) level is essential. The classic method of preparation for RAI therapy is thyroid hormone withdrawal (THW). However, the application of THW usually results in some physical or psychological side effects associated with hypothyroidism, such as general oedema, constipation and depression. Evidence indicates that hypothyroidism may affect liver function or structure directly. Therefore, the identification of factors that may cause 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.

MATERIALS AND METHODS

Participants or criteria selection
The study included 996 patients (314 men, 682 women; 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, hyperlipoidemia, etc.7

**Patient and public involvement**
This was an uncontrolled retrospective study; patients of this study had undergone RAI therapy at our department, and we recorded and analysed the data in order to investigate the risk factors for patients with hepatic dysfunction.

**Data collection and grouping**
All RAI therapy regimens were conducted by the same nuclear medicine department following a standard protocol (2015 ATA Management Guidelines). Relevant data were recorded during the RAI therapy, including patient age (named X1), sex (X2), the time between surgery and 131I therapy (X3), the presence or absence of metastases (lymph node metastasis or lung metastasis) (X4), the presence or absence of Hashimoto’s thyroiditis (X5), serum free triiodothyronine (FT3), total cholesterol (TC), and triglycerides (TG) (X6), and antithyroglobulin antibody (X7). The results showed that for male patients, the THW time, serum lipids, and liver function indices of the 996 patients were compared using bivariate logistic univariate regression analysis. In our study, 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 two groups (table 1). In the metastases group, the numbers of patients with hepatic dysfunction and lymph node metastasis or lung metastasis were 508 and 21, respectively; and the numbers of patients without hepatic dysfunction were 252 (315 of 315), 20.0% (63 of 315), and 0% (0 of 315), respectively.

**RESULTS**

**Clinical features of hepatic dysfunction**
Overall, 31.6% (315 of 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 of 315), 20.0% (63 of 315), and 0% (0 of 315), respectively.

**Risk factors for hepatic dysfunction in patients with DTC**
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 two groups (table 1). In the metastases group, the numbers of patients with hepatic dysfunction and lymph node metastasis or lung metastasis were 508 and 21, respectively; and the numbers of patients without hepatic dysfunction were 252 (315 of 315), and 12 (with lung metastasis), respectively. The results showed that for male patients, the THW time, FT1 <2.01 pmol/L, FT4 <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 (OR: 0.324–3.171, all p<0.01).

Furthermore, the multivariate logistic regression analysis was applied to screen the relevant risk factors. In our study, we suggested the following assignments for independent variables: X1=1 for age ≤45 years and X1=2 for age >45 years; X2=1 for male sex and X2=2 for female sex; X3=1 if the time between total thyroidectomy and 131I therapy was less than 3 months and X3=2 if the time between total thyroidectomy and 131I therapy was more than 3 months; X4=1, 2, and 3 if the THW time was shorter than 3 weeks, 3–4 weeks, and longer than 4 weeks, respectively; X5=1 (Hitachi Model 7170 analyser; Hitachi, Tokyo, Japan). The dosage range of 131I therapy was 3.7–7.4 GBq.

**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 131I therapy to evaluate their liver function.

**Statistical analysis**
A X2 test was used to analyse 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 variable p<0.05, and values p<0.05 were considered statistically significant. The OR was used to evaluate the risk factor. Statistical analysis was performed using SPSS for Windows, V.20.
for the presence of metastases and $X_6=2$ for the absence of metastases; $X_7=1$ for the presence of Hashimoto’s thyroiditis and $X_7=2$ for the absence of Hashimoto’s thyroiditis; $X_8=1, 2, 3,$ and $4$ for FT3 levels lower than 2.01 pmol/L, 2.01–2.37 pmol/L, and higher than 2.37 pmol/L, respectively; $X_9=1, 2, 3,$ and $4$ for TSH levels lower than 4.78 mIU/mL, 4.78–5.79 mIU/mL, and higher than 5.79 mIU/mL, respectively; $X_{10}=1, 2, 3,$ and $4$ for FT4 levels lower than 3.80 pmol/L, 3.80–4.78 pmol/L, and higher than 4.78 pmol/L; $X_{11}=1$ 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 7.22 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.

**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 of 315). Liver function test results revealed that 90.07% (227 of 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 of 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 of 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 75 mg (25 mg three times per day), the treated group) returned to normal after 1 month of $^{131}$I therapy. Moreover, the remission...
rate among patients in the untreated group was found to be 88.94% (177 of 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 150 mg (50 mg three times per day)), and the remission rates among patients at 1 month, 2 months, and 3 months after 131I therapy were 55.56% (35 of 63), 36.5% (23 of 63), and 7.94% (5 of 63), respectively. The average time for liver function to return to normal level in patients with moderate hepatic dysfunction was 1.8 months.

### DISCUSSION

A complex relationship between the thyroid gland and the liver exists in both healthy and disease states. Malik’s research showed that thyroid dysfunction may affect liver function. It is suggested that a relationship may exist between non-alcoholic fatty liver disease (NAFLD) and thyroid dysfunction. Several studies conducted in some countries worldwide showed that the relationship between levels of thyroid hormones and the incidence of NAFLD was inverse. In clinical practice, we have found that hepatic dysfunction in patients with DTC is common, and most of these patients have no obvious symptoms. The mechanism may be related to the following factors:

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 AST 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

#### Table 2

<table>
<thead>
<tr>
<th>Causal variable</th>
<th>B</th>
<th>SE</th>
<th>Wald</th>
<th>df</th>
<th>P value</th>
<th>Exp (B)</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>X9 (FT4)</td>
<td>-0.347</td>
<td>0.193</td>
<td>3.249</td>
<td>1</td>
<td>0.071</td>
<td>0.707</td>
<td>0.485 to 1.031</td>
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<tr>
<td>X9 (2)</td>
<td>-0.853</td>
<td>0.200</td>
<td>18.146</td>
<td>1</td>
<td>0.000</td>
<td>0.426</td>
<td>0.288 to 0.631</td>
</tr>
<tr>
<td>X9 (3)</td>
<td>-1.789</td>
<td>0.239</td>
<td>55.817</td>
<td>1</td>
<td>0.000</td>
<td>0.167</td>
<td>0.105 to 0.267</td>
</tr>
<tr>
<td>Constant</td>
<td>15.195</td>
<td>3</td>
<td>0.002</td>
<td>1</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

DTC, differentiated thyroid carcinoma; FT4, free thyroxine.

#### Table 3

<table>
<thead>
<tr>
<th>Degree</th>
<th>n</th>
<th>Remission (n (%))</th>
<th>Non-remission (n (%))</th>
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</thead>
<tbody>
<tr>
<td>Mild</td>
<td>252</td>
<td>227 (90.07)</td>
<td>25 (9.93)</td>
</tr>
<tr>
<td>Moderate</td>
<td>63</td>
<td>45 (71.43)</td>
<td>18 (28.57)</td>
</tr>
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χ² = 14.873, P value = 0.000

#### Table 4

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Remission (n (%))</th>
<th>Non-remission (n (%))</th>
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</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>53</td>
<td>50 (94.34)</td>
<td>3 (5.66)</td>
</tr>
<tr>
<td>No treatment</td>
<td>199</td>
<td>177 (88.94)</td>
<td>22 (11.06)</td>
</tr>
</tbody>
</table>

χ² = 1.765, P value = 0.184
related to cholestatic jaundice due to decreased bilirubin and bile excretion\textsuperscript{13}, and (4) severe hypothyroidism is known to cause increased permeability of the vascular endothelium\textsuperscript{14}. 

Our study demonstrated that 31.6% of patients with DTC 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 hypertriglyceridaemia and a higher FT\textsubscript{3}/FT\textsubscript{4} ratio are independent risk factors for NAFLD; however, hypothyroidism is not related to the condition directly.\textsuperscript{15} However, their research subjects were patients with hypothyroidism, where hypothyroidism was defined only by a TSH level ≥4.1 mIU/L, and FT\textsubscript{3} and FT\textsubscript{4} levels were not included. The FT\textsubscript{3} and FT\textsubscript{4} levels of some patients were normal.

To explore the risk factors of hepatic dysfunction for patients with DTC, we analysed 13 related factors, and found that male sex, a THW time greater than 21 days, FT\textsubscript{3} <2.01 pmol/L, FT\textsubscript{4} <1.78 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 (p<0.01). Additionally, we found that male sex, FT\textsubscript{3} <3.80 pmol/L and TG ≥1.28 mmol/L were closely associated with hepatic dysfunction in patients with DTC in the multivariate logistic regression analysis (p<0.01).

No other studies related to our study on the risk factors of hepatic dysfunction for patients with DTC 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 \textsuperscript{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\textsubscript{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 \textsuperscript{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.\textsuperscript{16}

Additionally, liver is the vital organ for cholesterol metabolism and thyroid hormones, which plays an important role in hepatic lipid metabolism.\textsuperscript{17} Thyroid hormones can increase the activity of lipid-lowering liver enzymes which can cause a reduction in low-density lipoprotein levels.\textsuperscript{18} As reported, serum lipids also play an important role in liver function,\textsuperscript{19} which coincided with the results of our study. In our study, hepatic function indices returned to normal at 1 month after \textsuperscript{131}I therapy in 86.54% 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 hyperlipidaemia and hepatic dysfunction was longer than that of the patients suffering from only hepatic 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 provide analysis of its influence 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\textsubscript{3} <2.01 pmol/L, FT\textsubscript{4} <1.78 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 patients with DTC with hepatic dysfunction before \textsuperscript{131}I therapy. For patients with DTC with hepatic dysfunction combined with dyslipidaemia, 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 \textsuperscript{131}I uptake when a patient with DTC undergoes RAI therapy. A number of patients suffer from general oedema, 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 ortholiposclerosis were found to have a higher likelihood of recovering to normal liver function. For men, FT\textsubscript{3} and TG levels were more closely related to hepatic dysfunction, and the prognosis of hepatic dysfunction was closely associated with the TG level.

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Contributors YJ and RW contributed to the conception and design of the study. YJ, WZ, JT and CW assisted with data acquisition. YJ, ZM and RW conducted the statistical analyses and drafted the manuscript. JT and ZM 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 is appropriately investigated and resolved. RW is the author responsible for the overall content as the guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Obtained.
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