Original article

Nuclear Medicine Communications

Influence of radioactive iodine therapy on liver function in patients with differentiated thyroid cancer

Sen Wang[a,b,*], Chao Liang[c,*], Li Zhao[c], Zhaowei Meng[a], Chunmei Zhang[a], Qiang Jia[a], Jian Tan[a], Hui Yang[b], Xiangxiang Liu[a] and Xiaoran Wang[a]

Aim **This study aimed to investigate the influence of radioactive iodine (RAI) therapy on liver function in patients with differentiated thyroid cancer (DTC), with emphasis on sex and dose accumulation.**

Patients and methods **Liver function after the first RAI ablation with ~3700 MBq (100 mCi) dosage was compared with baseline liver function in 357 patients with DTC (male: 110 and female: 247). Further comparisons were conducted in patients after regular and successive RAI therapies with available data, 126 patients (male: 37 and female: 89) with two RAI therapies, 52 patients (male: 16 and female: 36) with three RAI therapies, and 19 patients (male: 5 and female: 14) with four RAI therapies. Analyses were performed to evaluate the potential effect of RAI on liver function, including total protein (TP), albumin (ALB), globulin (GLO), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), γ-glutamyltransferase (GGT), lactic dehydrogenase, total bilirubin (TBIL), and direct bilirubin (DBIL) in both sexes. Continuous variables were analyzed by using nonparametric analysis.**

Results **Compared with the original hepatic function, TP ($P < 0.01$), ALB ($P < 0.05$), GLO ($P < 0.01$), ALT ($P < 0.05$), ALP ($P < 0.01$), and GGT ($P < 0.01$) declined significantly after the first RAI ablation in both sexes. TP, GLO, and GGT declined significantly in both sex subgroups, whereas ALT ($P < 0.05$), ALP ($P < 0.01$), and lactate dehydrogenase ($P < 0.05$) showed significant decline in male subgroup, and TBIL ($P < 0.05$) in female subgroup. As to the level of liver function after the second RAI therapy, TP ($P < 0.01$), GLO ($P < 0.01$), ALP ($P < 0.01$), GGT ($P < 0.01$), and DBIL ($P < 0.05$) showed a significant decreasing trend. In both sex subgroups, TP, GLO, and GGT reduced significantly. Moreover, only ALP ($P < 0.01$) significantly decreased in the male subgroup. As to the level of liver function after the third RAI therapy session, TP ($P < 0.01$) and GLO ($P < 0.01$) reduced significantly, whereas DBIL ($P < 0.05$) was higher than the original level. In sex subgroups, TP ($P < 0.05$) decreased significantly in the male subgroup, and GLO ($P < 0.01$) decreased significantly in the female subgroup, but DBIL ($P < 0.05$) increased significantly in the female subgroup. As to the level of liver function after the fourth RAI therapy, TBIL ($P < 0.05$) and DBIL ($P < 0.01$) increased significantly. In sex subgroups, TBIL ($P < 0.05$) and DBIL (2.09 ± 0.92 vs. 2.91 ± 1.14 μmol/l, $P < 0.05$) showed an increasing trend in the female subgroup only.**

Conclusion **Liver function of patients with DTC after the first RAI ablation decreased significantly, including TP, ALB, GLO, ALT, ALP, and GGT. However, after multiple and regular RAI therapies, TBIL and DBIL showed an increasing trend. Particularly, TBIL and DBIL showed an increasing trend in the female subgroup only.** *Nucl Med Commun* **00:000–000**

Nuclear Medicine Communications 2018, **00**:000–000

Keywords: differentiated thyroid cancer, liver function, radioactive iodine

[a]Department of Nuclear Medicine, Tianjin Medical University General Hospital, [b]Department of Nuclear Medicine, Affiliated Tumor Hospital of Zhengzhou University, Zhengzhou and [c]Department of Biochemistry and Molecular Biology, School of Basic Medical Sciences, Tianjin Medical University, Tianjin, People's Republic of China

Correspondence to Zhaowei Meng, MD, PhD, Department of Nuclear Medicine, Tianjin Medical University General Hospital, Anshan Road No. 154, Heping District, 300052 Tianjin, People's Republic of China
Tel: +86 186 2203 5159; fax: +86 222 781 3550;
e-mail: jamesmencius@163.com

*Sen Wang and Chao Liang contributed equally to the writing of this article.

Received 31 May 2018 **Revised** 27 August 2018 **Accepted** 4 September 2018

Introduction

Differentiated thyroid cancer (DTC) is one of the most common malignancy and is becoming increasingly prevalent. Overall, 28 per 100 000 populations experience DTC in the USA [1]. Radioactive iodine (RAI) therapy following thyroidectomy is recommended for most patients with DTC [2]. Although RAI therapy is generally safe, a large amount of studies present different degrees of potential adverse effects [3], including gastrointestinal symptoms [4], salivary gland dysfunction [5], bone marrow suppression [6], hematologic abnormalities [7], nasolacrimal obstruction [8], and even secondary malignancies [9]. However, studies about the influence of RAI therapy on liver function in patients with DTC are rare. Therefore, this study evaluated the potential effect of RAI therapy after traditional thyroid hormone withdrawal (THW) on liver function, with emphasis on sex and accumulated dose.

DOI: 10.1097/MNM.0000000000000919

Patients and methods

Patients

In our retrospective review, a consecutive series of 357 patients with DTC was evaluated, from the year 2012 to 2016, undergoing RAI therapy at least once (2960–4625 MBq). Hepatic function indexes were available in their medical record both at the time of each RAI therapy (after total thyroidectomy) and at the time of the first diagnostic whole-body scan. Patients were excluded from this study if they accorded with the following criteria: taking any medications that might affect liver function, known to have disease history of hepatic diseases, received a RAI therapeutic dose out of range (2960–4625 MBq), received external beam radiation therapy, and received chemotherapy within the entire process of thyroid cancer treatment. In addition, further comparisons were done in 126 patients (male: 37 and female: 89) for two RAI therapies, 52 patients (male: 16 and female: 36) for three RAI therapies, and 19 patients (male: 5 and female: 14) for four RAI therapies. Our study received approval from the Institutional Ethical Review Board.

Protocol

A total of 357 patients with DTC needed to perform THW preparation before RAI therapy. In other words, patients were asked to follow a low-iodine diet to control the intake of iodine, until 1 month later after RAI therapy. Moreover, levothyroxine withdrawal was performed for 3–4 weeks before RAI therapy. RAI was taken orally. Post-therapy whole-body scan was performed 3–5 days later. The specific activity was selected depending on the pathological pattern, the extent of regional and distant neoplasm metastases, the post-therapy whole-body scans, age, and cardiac function of each patients. The liver function test was assayed less than 3 days before taking RAI orally. Regular and successive RAI therapies were performed ~6 months after the previous RAI therapy when hepatic parameters were re-examined.

Parameter measurement

All liver function tests were assayed in the hematology laboratory at Tianjin Medical University General Hospital using an autoanalyzer (Hitachi Model 7600 analyzer; Hitachi, Tokyo, Japan). The normal ranges for parameters were as follows: total protein (TP), 62.00–85.00 g/l; albumin (ALB), 35.00–55.00 g/l; globulin (GLO), 20.00–40.00 g/l; alanine aminotransferase (ALT), 5.00–40.00 U/l; aspartate aminotransferase (AST), 8.00–40.00 U/l; alkaline phosphatase (ALP), 40.00–150.00 U/l; γ-glutamyltransferase (GGT), 7.00–49.00 U/l; lactic dehydrogenase (LDH), 94.00–250.00 U/l; total bilirubin (TBIL), 3.40–20.00 μmol/l; and direct bilirubin (DBIL), 0.10–6.80 μmol/l.

Statistical analysis

All data were presented as mean ± SD. Paired *t*-tests and nonparametric analysis were used to compare the continuous variables. *P* values less than 0.05 were considered significant. All statistical analyses were conducted by using Statistical Product and Service Solutions (SPSS version 17.0, Chicago, Illinois, USA).

Results

Clinical characteristics

The majority of the 357 (69.19%) patients with DTC were females, which was higher than males (30.81%). The age range of those patients was 19–76 years, with a mean age of 45.69 years. All patients had gone through total thyroidectomy for papillary thyroid cancer (90.20%) predominantly and follicular variant of papillary thyroid cancer (8.68%). The median administered RAI dose was 3774 MBq (range: 2960–4625 MBq) (Table 1).

Liver function findings after the first radioactive iodine therapy

The findings of liver function before and after the first RAI therapy (cumulative doses: ~3700 MBq) are shown in Tables 2 and 3. Compared with the preablation liver function, TP ($P < 0.01$), ALB ($P < 0.05$), GLO ($P < 0.01$), ALT ($P < 0.05$), ALP ($P < 0.01$), and GGT ($P < 0.01$) presented a significant decrease after the first RAI therapy. However, there was no statistically significant change of AST, LDH, TBIL, and DBIL after the first RAI therapy (Table 2).

Patients receiving the first RAI therapy were divided into groups according to their sexes. In male subgroup, TP ($P < 0.01$), GLO ($P < 0.01$), ALT ($P < 0.05$), ALP ($P < 0.01$), GGT ($P < 0.01$), and LDH ($P < 0.05$) showed a significant decrease after the first RAI therapy, but ALB, AST, TBIL, and DBIL appeared to have no statistical significance. In female subgroup, TP ($P < 0.01$), GLO ($P < 0.01$), GGT ($P < 0.01$), and TBIL ($P < 0.05$) declined significantly, but ALB, ALT, AST, ALP, LDH, and DBIL showed no significant changes after the first RAI therapy (Table 3).

Table 1 Baseline characteristics of the patients

Classification	Composition
Sex [*n* (%)]	
Male	110 (30.81)
Female	247 (69.19)
Age at RAI treatment (years)	
Median	47
Range	19–76
Mean ± SD	45.69 ± 12.14
Extent of surgery [*n* (%)]	
Total thyroidectomy	357 (100)
Histology [*n* (%)]	
PTC	322 (90.20)
FVPTC	31 (8.68)
FTC	4 (1.12)
HCC	0
Administered activity (mCi)	
Mean ± SD	3811 ± 209
Median	3774
Range	2960–4625

FTC, follicular thyroid cancer; FVPTC, follicular variant of papillary thyroid cancer; HCC, Hurthle cell cancer; PTC, papillary thyroid cancer; RAI, radioactive iodine.

Liver function findings after the second radioactive iodine therapy

Results of liver function findings before the initial RAI therapy and after the second RAI therapy (cumulative doses: ~7400 MBq) are shown in Tables 4 and 5. Compared with the preablation liver function, the levels of TP ($P < 0.01$), GLO ($P < 0.01$), ALP ($P < 0.01$), GGT ($P < 0.01$), and DBIL

Table 2 Liver function before and after the first radioactive iodine remnant ablation for all patients

	Before RAI ablation (mean ± SD)	6 months after RAI ablation (mean ± SD)	△ (mean ± SD)	*P* value[a]
TP (g/l)	75.85 ± 4.29	74.29 ± 5.49	−1.56 ± 5.77	0.000**
ALB (g/l)	46.95 ± 3.05	46.63 ± 3.20	−0.32 ± 3.50	0.048*
GLO (g/l)	28.95 ± 3.75	27.87 ± 3.55	−1.08 ± 3.04	0.000**
ALT (U/l)	29.82 ± 25.28	27.11 ± 18.29	−2.71 ± 25.18	0.039*
AST (U/l)	26.53 ± 14.44	25.36 ± 12.37	−1.17 ± 14.82	0.340
ALP (U/l)	63.26 ± 18.24	61.07 ± 17.15	−2.20 ± 11.69	0.000**
GGT (U/l)	28.33 ± 21.82	25.03 ± 18.30	−3.30 ± 15.47	0.000**
LDH (U/l)	201.20 ± 45.98	197.98 ± 41.40	−3.22 ± 42.93	0.259
TBIL (μmol/l)	10.21 ± 5.02	10.12 ± 6.49	−0.09 ± 5.99	0.126
DBIL (μmol/l)	3.22 ± 1.40	3.25 ± 1.34	0.03 ± 1.20	0.679

ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DBIL, direct bilirubin; GGT, γ-glutamyltransferase; GLO, globulin; LDH, lactate dehydrogenase; RAI, radioactive iodine; TBIL, total bilirubin; TP, total protein.
[a]Comparison between baseline and follow-up by paired *t*-test.
*$P < 0.05$.
**$P < 0.01$.

Table 3 Liver function before and after the first radioactive iodine remnant ablation according to sex

Sex	Before RAI ablation (mean ± SD)	First RAI ablation (mean ± SD)	△ (mean ± SD)	*P* value[a]
TP (g/l)				
Male	76.10 ± 4.02	74.18 ± 3.83	−1.92 ± 4.23	0.000**
Female	75.73 ± 4.41	74.34 ± 6.09	−1.39 ± 6.34	0.000**
ALB (g/l)				
Male	47.65 ± 3.26	47.17 ± 3.00	−0.47 ± 3.14	0.085
Female	46.64 ± 2.91	46.39 ± 3.26	−0.26 ± 3.66	0.224
GLO (g/l)				
Male	28.46 ± 3.67	26.98 ± 3.47	−1.47 ± 3.03	0.000**
Female	29.17 ± 3.77	28.27 ± 3.52	−0.90 ± 3.03	0.000**
ALT (U/l)				
Male	39.28 ± 24.55	34.99 ± 21.96	−4.29 ± 24.31	0.042*
Female	25.61 ± 24.50	23.60 ± 15.17	−2.01 ± 25.58	0.283
AST (U/l)				
Male	29.99 ± 15.74	27.80 ± 12.09	−2.19 ± 14.78	0.260
Female	24.99 ± 13.58	24.28 ± 12.36	−0.71 ± 14.84	0.633
ALP (U/l)				
Male	63.33 ± 15.74	59.62 ± 14.61	−3.71 ± 10.06	0.000**
Female	63.24 ± 19.28	61.71 ± 18.16	−1.52 ± 12.30	0.074
GGT (U/l)				
Male	35.35 ± 21.93	30.34 ± 18.45	−5.01 ± 13.72	0.000**
Female	25.21 ± 21.08	22.66 ± 17.77	−2.54 ± 16.15	0.001**
LDH (U/l)				
Male	209.76 ± 51.43	199.71 ± 43.50	−10.06 ± 47.08	0.027*
Female	197.39 ± 42.90	197.21 ± 40.50	−0.18 ± 40.69	0.780
TBIL (μmol/l)				
Male	11.83 ± 5.94	12.68 ± 9.79	0.85 ± 8.99	0.631
Female	9.49 ± 4.38	8.97 ± 3.78	−0.51 ± 3.93	0.028*
DBIL (μmol/l)				
Male	3.71 ± 1.68	3.72 ± 1.63	0.01 ± 1.17	0.680
Female	3.01 ± 1.20	3.04 ± 1.13	0.03 ± 1.21	0.845

ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DBIL, direct bilirubin; GGT, γ-glutamyltransferase; GLO, globulin; LDH, lactate dehydrogenase; RAI, radioactive iodine; TBIL, total bilirubin; TP, total protein.
[a]Comparison between baseline and follow-up by nonparametric analysis.
*$P < 0.05$.
**$P < 0.01$.

Table 4 Liver function after first and second radioactive iodine treatments for all patients

	Before RAI ablation (mean ± SD)	First RAI ablation (mean ± SD)	*P* value[a]	Second RAI therapy (mean ± SD)	*P* value[a]
TP (g/l)	76.19 ± 4.39	74.58 ± 7.32	0.006**	74.56 ± 4.02	0.000**
ALB (g/l)	46.66 ± 3.14	46.65 ± 2.81	0.829	46.33 ± 2.92	0.389
GLO (g/l)	29.53 ± 3.85	28.40 ± 3.58	0.000**	28.24 ± 3.29	0.000**
ALT (U/l)	27.49 ± 18.64	26.31 ± 17.65	0.463	24.23 ± 13.55	0.066
AST (U/l)	25.11 ± 12.29	25.71 ± 10.74	0.379	22.80 ± 7.54	0.058
ALP (U/l)	68.47 ± 21.01	64.79 ± 17.65	0.001**	65.63 ± 21.20	0.004**
GGT (U/l)	28.98 ± 21.47	27.90 ± 24.72	0.034*	25.71 ± 24.97	0.000**
LDH (U/l)	199.86 ± 49.16	201.98 ± 44.59	0.488	210.45 ± 151.87	0.601
TBIL (μmol/l)	9.79 ± 5.45	10.23 ± 5.27	0.610	9.72 ± 5.22	0.795
DBIL (μmol/l)	2.96 ± 1.57	3.20 ± 1.54	0.064	3.19 ± 1.50	0.043*

ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DBIL, direct bilirubin; GGT, γ-glutamyltransferase; GLO, globulin; LDH, lactate dehydrogenase; RAI, radioactive iodine; TBIL, total bilirubin; TP, total protein.
[a]Compassion of changes between males and females by nonparametric analysis.
*$P < 0.05$.
**$P < 0.01$.

Table 5 Liver function after first and second radioactive iodine treatments according to sex

Sex	Before RAI ablation (mean ± SD)	First RAI ablation (mean ± SD)	*P* value[a]	Second RAI therapy (mean ± SD)	*P* value[a]
TP (g/l)					
Male	76.14 ± 4.47	74.76 ± 3.77	0.053	74.30 ± 4.56	0.013*
Female	76.21 ± 4.37	74.51 ± 8.39	0.047*	74.67 ± 3.79	0.007**
ALB (g/l)					
Male	47.81 ± 3.62	47.78 ± 3.10	1.000	47.46 ± 3.28	0.549
Female	46.18 ± 2.80	46.18 ± 2.55	0.763	45.85 ± 2.64	0.512
GLO (g/l)					
Male	28.32 ± 3.90	26.89 ± 3.53	0.012*	26.84 ± 3.32	0.015*
Female	30.03 ± 3.73	29.03 ± 3.43	0.011*	28.82 ± 3.11	0.002**
ALT (U/l)					
Male	38.30 ± 25.15	36.41 ± 20.50	0.623	30.62 ± 16.77	0.078
Female	23.00 ± 12.85	22.11 ± 14.40	0.529	21.57 ± 11.02	0.265
AST (U/l)					
Male	28.76 ± 17.73	30.57 ± 13.31	0.271	25.05 ± 9.11	0.441
Female	23.60 ± 8.83	23.70 ± 8.80	0.929	21.87 ± 6.61	0.064
ALP (U/l)					
Male	67.84 ± 15.01	61.78 ± 12.50	0.001**	63.05 ± 16.97	0.004**
Female	68.73 ± 23.12	66.03 ± 19.32	0.074	66.71 ± 22.73	0.124
GGT (U/l)					
Male	39.84 ± 26.93	32.30 ± 19.10	0.002**	33.41 ± 22.36	0.009**
Female	24.46 ± 16.96	26.07 ± 26.59	0.696	22.52 ± 25.42	0.001**
LDH (U/l)					
Male	195.73 ± 40.97	200.68 ± 32.86	0.284	194.89 ± 36.99	0.769
Female	201.57 ± 52.31	202.53 ± 48.80	0.885	216.92 ± 179.05	0.392
TBIL (μmol/l)					
Male	12.96 ± 7.98	13.47 ± 6.88	0.541	13.09 ± 6.95	0.577
Female	8.47 ± 3.19	8.88 ± 3.73	0.832	8.31 ± 3.49	0.440
DBIL (μmol/l)					
Male	3.94 ± 2.21	4.05 ± 2.01	0.228	4.11 ± 1.96	0.365
Female	2.55 ± 0.97	2.85 ± 1.13	0.128	2.80 ± 1.07	0.068

ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DBIL, direct bilirubin; GGT, γ-glutamyltransferase; GLO, globulin; LDH, lactate dehydrogenase; RAI, radioactive iodine; TBIL, total bilirubin; TP, total protein.
[a]Compassion of changes between males and females by nonparametric analysis.
*$P < 0.05$.
**$P < 0.01$.

($P < 0.05$) fell off significantly after the second RAI therapy, but the changes of ALB, ALT, AST, LDH, and TBIL presented no statistical significance (Table 4).

In male subgroup, TP ($P < 0.05$), GLO ($P < 0.05$), ALP ($P < 0.01$), and GGT ($P < 0.01$) showed a significant decrease after the second RAI therapy, whereas ALB, ALT, AST, LDH, TBIL, and DBIL showed no significance changes after the second RAI therapy. In female subgroup, TP ($P < 0.01$), GLO ($P < 0.01$), and GGT ($P < 0.01$) presented a significant decrease after the second RAI therapy. However, there were no statistical significances in ALB, ALT, AST, ALP, LDH, TBIL, and DBIL after the second RAI therapy (Table 5).

Liver function findings after the third radioactive iodine therapy

Results of liver function findings before the initial RAI therapy and after the third RAI therapy (cumulative doses: ~11 100 MBq) are shown in Tables 6 and 7. Compared with the preablation liver function, TP ($P < 0.01$) and GLO ($P < 0.01$) presented a significant decrease after the third RAI therapy, whereas DBIL ($P < 0.05$) presented a significant increase. There were no statistical significance in ALB, ALT, AST, ALP, GGT, LDH, and TBIL (Table 6).

In male subgroup, only TP ($P < 0.05$) showed a significant decrease, but there were not significant changes in ALB, GLO, ALT, AST, ALP, GGT, LDH, TBIL, and DBIL. In female subgroup, only GLO ($P < 0.01$) decreased significantly, but DBIL ($P < 0.05$) increased significantly. TP, ALB, ALT, AST, ALP, GGT, LDH, and TBIL presented no statistical significance after the third RAI therapy (Table 7).

Liver function findings after the fourth radioactive iodine therapy

Results of liver function findings before the initial RAI therapy and after the fourth RAI therapy (cumulative doses: ~14 800 MBq) are shown in Tables 8 and 9. Compared with the preablation liver function, only TBIL ($P < 0.05$) and DBIL ($P < 0.01$) presented a significant increase. There was no significant difference in TP, ALB, GLO, ALT, AST, ALP, GGT, and LDH (Table 8).

In the male subgroup, all parameters with regard to liver function showed no significant difference, whereas in the female subgroup, TBIL ($P < 0.05$) and DBIL ($P < 0.05$) presented a significant increase. There was no significant difference in TP, ALB, GLO, ALT, AST, ALP, GGT, and LDH after the fourth RAI therapy (Table 9).

Discussion

RAI therapy is a common therapeutic means used in patients with DTC after thyroidectomy, for the ablation of postsurgical thyroid remnant [10], and interrelated changes in physiological status of patients with thyroid cancer after RAI therapy were reported in a large number of studies [5,7,11,12]. In our study, some parameters (hepatic enzymes) about liver function of patients with DTC changed significantly after the first RAI therapy, which indicated that RAI therapy had an influence on liver function. As we all know, the key mechanism of RAI therapy was the biological effect of ionizing radiations that RAI generated. Moreover, some fundamental research studies showed that radioactive radiation, like ionizing radiations and radiographs, had a significant effect on body systems of humans and animals [13,14]. Studies displayed that there were changes in hepatocyte growth factor and hepatocellular mRNA levels with body irradiation [15–17]. Our study also found that there were no significant changes in hepatic enzymes after undergoing three RAI therapy sessions or even more RAI therapy sessions, that was, there were no significant dose–response relationship detected in hepatic enzymes. However, Nwokocha *et al.* [18] presented that hepatic enzymes were compromised with excess total-body irradiation.

Conventional RAI therapy required THW or recombinant human thyroid-stimulating hormone (rhTSH) stimulation before RAI therapy to elevate endogenous TSH levels, which was essential for RAI therapy because it promoted both radioiodine uptake and retention in the residual

Table 6 Liver function after first, second, and third radioactive iodine treatments for all patients

	Before RAI ablation (mean ± SD)	First RAI ablation (mean ± SD)	*P* value[a]	Second RAI therapy (mean ± SD)	*P* value[a]	Third RAI therapy (mean ± SD)	*P* value[a]
TP (g/l)	76.77 ± 4.16	75.27 ± 4.16	0.024*	75.12 ± 3.52	0.014*	73.94 ± 10.08	0.009**
ALB (g/l)	47.04 ± 3.34	46.44 ± 3.12	0.329	46.23 ± 2.53	0.268	47.48 ± 4.91	0.988
GLO (g/l)	29.73 ± 3.80	28.83 ± 3.39	0.031*	28.88 ± 3.25	0.114	28.71 ± 4.37	0.002**
ALT (U/l)	27.63 ± 22.97	27.69 ± 22.30	0.916	25.37 ± 19.18	0.186	23.85 ± 14.09	0.247
AST (U/l)	25.52 ± 14.71	26.08 ± 11.11	0.379	23.88 ± 8.98	0.425	24.12 ± 9.06	0.636
ALP (U/l)	68.15 ± 18.34	65.50 ± 19.22	0.044*	67.63 ± 24.03	0.212	68.67 ± 24.24	0.985
GGT (U/l)	28.69 ± 22.66	29.15 ± 29.07	0.401	28.71 ± 33.10	0.047*	32.29 ± 40.77	0.980
LDH (U/l)	192.63 ± 56.94	195.75 ± 43.93	0.278	230.29 ± 232.06	0.253	185.02 ± 38.01	0.629
TBIL (μmol/l)	9.19 ± 3.98	9.48 ± 4.90	0.953	9.42 ± 4.14	0.715	13.87 ± 32.95	0.914
DBIL (μmol/l)	2.70 ± 1.56	2.87 ± 1.57	0.329	3.00 ± 1.40	0.041*	3.22 ± 1.67	0.012*

ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DBIL, direct bilirubin; GGT, γ-glutamyltransferase; GLO, globulin; LDH, lactate dehydrogenase; RAI, radioactive iodine; TBIL, total bilirubin; TP, total protein.

[a]Compassion of changes between males and females by nonparametric analysis.

*$P < 0.05$.

**$P < 0.01$.

Table 7 Liver function after first, second, and third radioactive iodine treatments according to sex

Sex	Before RAI ablation (mean ± SD)	First RAI ablation (mean ± SD)	*P* value[a]	Second RAI therapy (mean ± SD)	*P* value[a]	Third RAI therapy (mean ± SD)	*P* value[a]
TP (g/l)							
Male	76.31 ± 3.91	74.38 ± 4.21	0.069	75.06 ± 3.57	0.302	70.50 ± 16.98	0.011*
Female	76.97 ± 4.30	75.67 ± 4.13	0.124	75.14 ± 3.56	0.033*	75.47 ± 4.08	0.117
ALB (g/l)							
Male	47.56 ± 3.52	46.19 ± 3.51	0.046*	46.31 ± 2.60	0.185	47.94 ± 8.20	0.122
Female	46.81 ± 3.29	46.56 ± 2.98	0.857	46.19 ± 2.53	0.634	47.28 ± 2.48	0.389
GLO (g/l)							
Male	28.75 ± 4.33	28.19 ± 3.45	0.510	28.75 ± 3.55	0.819	29.88 ± 6.09	0.977
Female	30.17 ± 3.59	29.11 ± 3.37	0.036*	28.94 ± 3.16	0.040*	28.19 ± 3.32	0.000**
ALT (U/l)							
Male	38.56 ± 34.32	41.19 ± 27.44	0.570	36.06 ± 28.03	1.000	30.19 ± 18.30	0.254
Female	22.78 ± 13.60	21.69 ± 16.78	0.459	20.61 ± 11.13	0.070	21.03 ± 10.92	0.486
AST (U/l)							
Male	26.94 ± 19.36	31.19 ± 15.34	0.244	26.19 ± 11.84	0.535	25.38 ± 9.72	0.955
Female	24.89 ± 12.39	23.81 ± 7.85	0.959	22.86 ± 7.34	0.159	23.56 ± 8.83	0.436
ALP (U/l)							
Male	67.75 ± 14.45	64.25 ± 18.01	0.093	70.00 ± 26.58	0.551	66.38 ± 20.78	0.679
Female	68.33 ± 20.01	66.06 ± 19.96	0.198	66.58 ± 23.13	0.272	69.69 ± 25.83	0.731
GGT (U/l)							
Male	35.88 ± 26.63	30.38 ± 23.29	0.293	34.81 ± 27.11	0.802	40.19 ± 40.43	0.975
Female	25.50 ± 20.25	28.61 ± 31.59	0.640	26.00 ± 35.45	0.023*	28.78 ± 40.99	0.922
LDH (U/l)							
Male	170.50 ± 35.87	180.44 ± 25.28	0.214	194.25 ± 34.17	0.066	176.69 ± 45.28	0.187
Female	202.47 ± 62.04	202.56 ± 48.83	0.683	246.31 ± 277.69	0.894	188.72 ± 34.36	0.118
TBIL (μmol/l)							
Male	10.51 ± 4.83	11.48 ± 6.47	0.587	11.12 ± 5.00	0.756	25.55 ± 58.71	0.587
Female	8.61 ± 3.45	8.59 ± 3.78	0.666	8.66 ± 3.505	0.800	8.68 ± 3.81	0.594
DBIL (μmol/l)							
Male	3.21 ± 2.34	3.29 ± 2.03	0.441	3.53 ± 1.91	0.468	3.94 ± 2.32	0.164
Female	2.47 ± 1.02	2.69 ± 1.31	0.457	2.77 ± 1.06	0.061	2.90 ± 1.19	0.029*

ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DBIL, direct bilirubin; GGT, γ-glutamyltransferase; GLO, globulin; LDH, lactate dehydrogenase; RAI, radioactive iodine; TBIL, total bilirubin; TP, total protein.
[a]Compassion of changes between males and females by nonparametric analysis.
*$P < 0.05$.
**$P < 0.01$.

Table 8 Liver function after first, second, third, and fourth radioactive iodine treatments for all patients

	Before RAI ablation (mean ± SD)	First RAI ablation (mean ± SD)	*P* value[a]	Second RAI therapy (mean ± SD)	*P* value[a]	Third RAI therapy (mean ± SD)	*P* value[a]	Fourth RAI therapy (mean ± SD)	*P* value[a]
TP (g/l)	77.37 ± 3.69	76.47 ± 3.37	0.496	75.95 ± 2.90	0.175	76.58 ± 3.56	0.360	76.47 ± 3.36	0.265
ALB (g/l)	46.74 ± 3.12	46.42 ± 2.04	0.965	46.47 ± 2.59	0.757	47.32 ± 3.07	0.481	46.74 ± 3.25	0.975
GLO (g/l)	30.63 ± 2.71	30.05 ± 2.22	0.493	29.47 ± 2.50	0.100	29.26 ± 2.64	0.051	29.74 ± 3.68	0.142
ALT (U/l)	23.53 ± 15.70	21.84 ± 8.19	0.758	23.16 ± 12.89	0.744	21.00 ± 8.97	0.856	18.37 ± 8.96	0.131
AST (U/l)	21.74 ± 6.56	22.68 ± 6.03	0.643	23.00 ± 7.08	0.631	21.95 ± 6.12	0.632	20.47 ± 5.92	0.545
ALP (U/l)	68.95 ± 15.54	68.95 ± 19.71	0.984	69.21 ± 22.78	0.705	74.58 ± 26.58	0.251	77.42 ± 27.37	0.083
GGT (U/l)	32.37 ± 25.56	34.00 ± 39.62	0.924	33.42 ± 47.03	0.118	36.47 ± 54.02	0.904	38.47 ± 51.97	0.913
LDH (U/l)	187.74 ± 41.29	193.11 ± 42.62	0.615	198.05 ± 43.67	0.259	187.32 ± 31.35	0.968	194.21 ± 36.62	0.198
TBIL (μmol/l)	7.90 ± 3.22	8.51 ± 3.28	0.259	9.69 ± 4.89	0.035*	8.45 ± 3.55	0.191	9.27 ± 3.07	0.018*
DBIL (μmol/l)	2.26 ± 0.95	2.62 ± 1.16	0.129	2.89 ± 1.56	0.025*	2.84 ± 1.22	0.030*	3.14 ± 1.13	0.007**

ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DBIL, direct bilirubin; GGT, γ-glutamyltransferase; GLO, globulin; LDH, lactate dehydrogenase; RAI, radioactive iodine; TBIL, total bilirubin; TP, total protein.
[a]Compassion of changes between males and females by nonparametric analysis.
*$P < 0.05$.
**$P < 0.01$.

functioning thyroid tissue. In our study, the patients receive RAI therapy with traditional THW, who sustained hypothyroidism state before and during the whole RAI therapy. In a state of hypothyroid before RAI therapy with THW, the levels of ALT and AST were higher than the preoperative levels. The levels of ALT and AST were lower than the preoperative levels in a state of euthyroid after RAI therapy with THW [19].

Our study evaluated the potential effect of RAI therapy after THW on liver function. Some significant results showed that bilirubin presented a significant increase after the third (~11 100 MBq) and fourth RAI therapy sessions (~148 100 MBq), and only presented in females in our study. However, some study reported that the patients with overt hypothyroidism would experience cholestatic hepatitis because of bile excretion and reduced bilirubin [20].

Table 9 Liver function after first, second, third, and fourth radioactive iodine treatments according to sex

Sex	Before RAI ablation (mean ± SD)	First RAI ablation (mean ± SD)	*P* value[a]	Second RAI therapy (mean ± SD)	*P* value[a]	Third RAI therapy (mean ± SD)	*P* value[a]	Fourth RAI therapy (mean ± SD)	*P* value[a]
TP (g/l)									
Male	75.40 ± 2.97	75.60 ± 3.36	0.785	76.00 ± 2.92	0.581	75.00 ± 2.74	0.593	74.40 ± 2.41	0.131
Female	78.07 ± 3.75	76.79 ± 3.45	0.360	75.93 ± 3.00	0.057	77.14 ± 3.74	0.422	77.21 ± 3.40	0.532
ALB (g/l)									
Male	45.80 ± 3.63	45.80 ± 2.86	1.000	47.80 ± 2.86	0.279	45.80 ± 4.71	0.892	45.20 ± 3.03	0.414
Female	47.07 ± 3.00	46.64 ± 1.74	0.975	46.00 ± 2.42	0.406	47.86 ± 2.25	0.374	47.29 ± 3.25	0.789
GLO (g/l)									
Male	29.60 ± 2.19	29.80 ± 2.49	0.713	28.20 ± 2.78	0.588	29.20 ± 3.11	1.000	29.20 ± 1.10	0.680
Female	31.00 ± 2.86	30.14 ± 2.21	0.282	29.93 ± 2.34	0.091	29.29 ± 2.59	0.009**	29.93 ± 4.27	0.160
ALT									
Male	22.80 ± 15.96	23.60 ± 9.31	0.684	21.80 ± 10.57	0.892	19.20 ± 8.35	0.686	18.60 ± 12.66	0.176
Female	23.79 ± 16.21	21.21 ± 8.03	0.937	23.64 ± 13.95	0.753	21.64 ± 9.39	0.851	18.29 ± 7.87	0.314
AST									
Male	19.60 ± 4.56	23.20 ± 9.15	0.345	23.80 ± 8.08	0.223	19.00 ± 5.52	0.715	18.80 ± 6.22	0.786
Female	22.50 ± 7.12	22.50 ± 4.94	0.975	22.71 ± 7.00	1.000	23.00 ± 6.16	0.550	21.07 ± 5.93	0.660
ALP									
Male	65.00 ± 19.20	57.40 ± 14.01	0.043*	58.20 ± 13.03	0.068	64.80 ± 13.24	0.500	64.80 ± 11.08	0.684
Female	70.36 ± 14.59	73.07 ± 20.20	0.258	73.14 ± 24.55	0.649	78.07 ± 29.58	0.209	81.93 ± 30.27	0.059
GGT									
Male	30.40 ± 30.58	25.00 ± 19.22	0.357	29.40 ± 22.87	0.715	32.60 ± 21.69	0.686	34.20 ± 25.18	0.893
Female	33.07 ± 24.80	37.21 ± 44.92	0.861	34.86 ± 53.79	0.100	37.86 ± 62.36	0.851	40.00 ± 59.46	0.972
LDH									
Male	188.20 ± 42.64	193.00 ± 56.84	0.500	197.60 ± 50.97	0.223	185.20 ± 21.51	0.686	190.60 ± 30.37	0.786
Female	187.57 ± 42.44	193.14 ± 39.00	0.753	198.21 ± 42.91	0.470	188.07 ± 34.87	0.753	195.50 ± 39.57	0.187
TBIL (μmol/l)									
Male	10.06 ± 3.81	9.56 ± 3.44	0.500	12.52 ± 3.32	0.138	10.24 ± 4.00	0.893	10.86 ± 3.80	0.345
Female	7.12 ± 2.74	8.13 ± 3.26	0.102	8.68 ± 5.06	0.116	7.81 ± 3.29	0.172	8.71 ± 2.69	0.016*
DBIL (μmol/l)									
Male	2.74 ± 0.98	2.98 ± 1.04	0.416	3.76 ± 0.96	0.039*	2.94 ± 1.13	0.893	3.76 ± 0.94	0.144
Female	2.09 ± 0.92	2.49 ± 1.20	0.182	2.58 ± 1.64	0.124	2.81 ± 1.28	0.015*	2.91 ± 1.14	0.030*

ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DBIL, direct bilirubin; GGT, γ-glutamyltransferase; GLO, globulin; LDH, lactate dehydrogenase; RAI, radioactive iodine; TBIL, total bilirubin; TP, total protein.

[a]Compassion of changes between males and females by nonparametric analysis.

*$P < 0.05$.

**$P < 0.01$.

In hypothyroidism state, bilirubin excretion decreases because of an increased hepatic bilirubin uridine 5′-diphospho-glucuronosyltransferase activity and a decreased p-nitrophenol uridine 5′-diphospho-glucuronosyltransferase, which lead to an increased total bilirubin concentration in the serum [21,22]. The specific mechanism might also be related to the changes of cytomembrane in hypothyroidism state. In uncomplicated hypothyroidism, the membrane cholesterol–phospholipid ratio and diminished membrane fluidity increase, which result in a reduction of bile flow [23,24].

The effect of RAI therapy on bilirubin presented dose–response relationship. After first RAI therapy, the liver functions, including TP, ALB, GLO, ALT, ALP, and GGT, were significantly lower compared with liver functions before RAI therapy, and those indexes of liver function were always in the normal range, which indicated the first RAI therapy had no effect on bilirubin. After the third or fourth RAI therapy sessions, most of the indicators of liver function did not change significantly, and only the bilirubin level increased significantly, and the range of bilirubin was always within the normal range. As we all know, the liver is a common visceral organ where RAI concentrate after RAI therapy [25,26]. Multiple high-dose RAI therapies mean multiple radiation exposure to the liver, which could result in various levels of liver damage. Bilirubin was regarded as antioxidant and protective agent against oxidative reactions in liver damage [27–29]. In this study, only bilirubin elevated after multiple high-dose RAI therapy, which presented the potential protection effect of bilirubin in patients with DTC after multiple RAI therapy.

C-reactive protein (CRP) was closely related to cardiometabolic risk and type 2 diabetes mellitus [30,31]. In the state of hypothyroidism, free thyroxine (fT4) was inversely proportional to high sensitive CRP (hsCRP) level, and serum bilirubin level was decreased when hsCRP level was increased [32,33]. We considered that our findings that bilirubin increased after multiple iodine treatments were also associated with this condition. In the latest guidelines, the time of THW was shortened, which changed from conventional 4 to 2 weeks shortest [10]. Therefore, the THW time in the fourth treatment was shorter than the time in initial treatment relatively, so the fT4 level in the fourth treatment might be higher than the fT4 level in initial treatment, and accordingly, the lower hsCRP level presented in the fourth treatment, which resulted in the slight increase of bilirubin.

Significant sex difference was showed on the effect of RAI therapy on liver function. Among healthy people, there

was a difference in bilirubin levels between men and women, and men had higher levels of bilirubin than women [34,35]. However, the rise of bilirubin after multiple RAI therapy only appeared in the female group; we considered the reason might be associated with the protective effect of estrogen [36]. In other words, the hepatic cells in the female subgroup were relatively less damaged after multiple RAI treatments, so hsCRP levels were lower in the female subgroup, further leading to increased bilirubin, which explains the increased bilirubin in the women group. Moreover, the specific mechanism was worthy of further study.

There were several limitations in our work. First, this study did not distinguish if the liver function in some individuals exceeded the normal range of liver function, and these individuals with abnormal liver function might affect the results. Second, we did not include lower dose (< 2960 MBq) for low-risk patients, and we would continue to optimize this study with more wide range of RAI doses in the future. Moreover, rhTSH stimulation before RAI therapy was not available in China, so we could not distinguish the difference between rhTSH and THW. Finally, the sample capacity of patients after the third and fourth RAI therapy was small, and we will collect more patients' data in the next step research.

Conclusion

Our study showed that after the first RAI administration, liver function, including TP, ALB, GLO, ALT, ALP, and GGT, decreased significantly. However, after multiple and regular RAI therapies (high accumulated dose), TBIL and DBIL showed an increasing trend. In sex subgroups, TBIL and DBIL showed an increasing trend only in the female subgroup. That is to say, the RAI therapy of high accumulated dose had no significant effect on bilirubin level of the males, whereas a significant increase was seen in the females.

Acknowledgements

This study was supported by the National Key Clinical Specialty Project (awarded to the Departments of Nuclear Medicine and Radiology).

This study was also supported by the Tianjin Medical University General Hospital New Century Excellent Talent Program; Young and Middle-aged Innovative Talent Training Program from Tianjin Education Committee; and Talent Fostering Program (the 131 Project) from Tianjin Education Committee, Tianjin Human Resources and Social Security Bureau (awarded to Zhaowei Meng); and by the China National Natural Science Foundation grant 81571709, Key Project of Tianjin Science and Technology Committee Foundation grant 16JCZDJC34300 (awarded to Zhaowei Meng).

Conflicts of interest

There are no conflicts of interest.

References

1 Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin* 2017; **67**:7–30.
2 Haugen BR, Sawka AM, Alexander EK, Bible KC, Caturegli P, Doherty GM, *et al.* American Thyroid Association Guidelines on the Management of Thyroid Nodules and Differentiated Thyroid Cancer Task Force Review and Recommendation on the Proposed Renaming of Encapsulated Follicular Variant Papillary Thyroid Carcinoma Without Invasion to Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features. *Thyroid* 2017; **27**:481–483.
3 Fard-Esfahani A, Emami-Ardekani A, Fallahi B, Fard-Esfahani P, Beiki D, Hassanzadeh-Rad A, Eftekhari M. Adverse effects of radioactive iodine-131 treatment for differentiated thyroid carcinoma. *Nucl Med Commun* 2014; **35**:808–817.
4 Kita T, Yokoyama K, Higuchi T, Kinuya S, Taki J, Nakajima K, *et al.* Multifactorial analysis on the short-term side effects occurring within 96 h after radioiodine-131 therapy for differentiated thyroid carcinoma. *Ann Nucl Med* 2004; **18**:345–349.
5 Upadhyaya A, Meng Z, Wang P, Zhang G, Jia Q, Tan J, *et al.* Effects of first radioiodine ablation on functions of salivary glands in patients with differentiated thyroid cancer. *Medicine (Baltimore)* 2017; **96**:e7164.
6 Prinsen HT, Klein Hesselink EN, Brouwers AH, Plukker JT, Jia Q, Tan J, *et al.* Bone marrow function after (131)I therapy in patients with differentiated thyroid carcinoma. *J Clin Endocrinol Metab* 2015; **100**:3911–3917.
7 Hu T, Meng Z, Zhang G, Jia Q, Tan J, Zheng W, *et al.* Influence of the first radioactive iodine ablation on peripheral complete blood count in patients with differentiated thyroid cancer. *Medicine (Baltimore)* 2016; **95**:e4451.
8 Kloos RT, Duvuuri V, Jhiang SM, Cahill KV, Foster JA, Burns JA. Nasolacrimal drainage system obstruction from radioactive iodine therapy for thyroid carcinoma. *J Clin Endocrinol Metab* 2002; **87**:5817–5820.
9 Brown AP, Chen J, Hitchcock YJ, Szabo A, Shrieve DC, Tward JD, *et al.* The risk of second primary malignancies up to three decades after the treatment of differentiated thyroid cancer. *J Clin Endocrinol Metab* 2008; **93**:504–515.
10 Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, *et al.* 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid* 2016; **26**:1–133.
11 He Y, Meng Z, Jia Q, Hu F, He X, Tan J, *et al.* Sleep quality of patients with differentiated thyroid cancer. *PLoS One* 2015; **10**:e0130634.
12 Liu N, Meng Z, Jia Q, Tan J, Zhang G, Zheng W, *et al.* Multiple-factor analysis of the first radioactive iodine therapy in post-operative patients with differentiated thyroid cancer for achieving a disease-free status. *Sci Rep* 2016; **6**:34915.
13 Nwokocha CR, Nwokocha MI, Mounmbegna PP, Owu DU, Onyezuligbo O, Olu-Osifo EH, *et al.* Serum lipids, proteins and electrolyte profiles in rats following total body irradiation. *West Indian Med J* 2012; **61**:117–121.
14 Chukwuemeka N, Philippe M, Magdalene N, Onyezuligbo O. Effects of total body irradiation on fatty acid and total lipid content of rats. *Pak J Pharm Sci* 2012; **25**:169–173.
15 Yamazaki H, Matsumoto K, Inoue T, Nose T, Murayama S, Teshima T, *et al.* Induction of hepatocyte growth factor in the liver, kidney and lung following total body irradiation in rat. *Cytokine* 1996; **8**:927–932.
16 Trutic N, Magic Z, Urosevic N, Krtolica K. Acute-phase protein gene expression in rat liver following whole body X-irradiation or partial hepatectomy. *Comp Biochem Physiol C Toxicol Pharmacol* 2002; **133**:461–470.
17 Meng Z, Tan J, Zhang G, Tian W, Fu Q, Li W, *et al.* Evaluation of serum midkine as a biomarker in differentiated thyroid cancer. *Life Sci* 2015; **130**:18–24.
18 Nwokocha CR, Nwokocha M, Mounmbegna P, Orhue J, Onyezuligbo O, Olu-Osifo EH, *et al.* Proteins and liver function changes in rats following cumulative total body irradiations. *West Indian Med J* 2012; **61**:773–777.
19 Lee SJ, Lee HY, Lee WW, Kim SE. The effect of recombinant human thyroid stimulating hormone on sustaining liver and renal function in thyroid cancer patients during radioactive iodine therapy. *Nucl Med Commun* 2014; **35**:727–732.
20 Volzke H, Robinson DM, John U. Association between thyroid function and gallstone disease. *World J Gastroenterol* 2005; **11**:5530–5534.
21 Van Steenbergen W, Fevery J, De Vos R, Leyten R, Heirwegh KP, De Groote J. Thyroid hormones and the hepatic handling of bilirubin. I. Effects of hypothyroidism and hyperthyroidism on the hepatic transport of bilirubin mono- and diconjugates in the Wistar rat. *Hepatology* 1989; **9**:314–321.
22 Malik R, Hodgson H. The relationship between the thyroid gland and the liver. *QJM* 2002; **95**:559–569.

23 Targher G, Montagnana M, Salvagno G, Moghetti P, Zoppini G, Muggeo M, Lippi G. Association between serum TSH, free T4 and serum liver enzyme activities in a large cohort of unselected outpatients. *Clin Endocrinol (Oxf)* 2008; **68**:481–484.

24 Arora S, Chawla R, Tayal D, Gupta VK, Sohi JS, Mallika V. Biochemical markers of liver and kidney function are influenced by thyroid function-a case-controlled follow up study in Indian hypothyroid subjects. *Indian J Clin Biochem* 2009; **24**:370–374.

25 Tatar FA, Morita E, Ituarte PH, Cavalieri RR, Duh QY, Price DC, *et al*. Association between residual thyroid carcinoma and diffuse hepatic uptake of ^{131}I following radioiodine ablation in postoperative total thyroidectomy patients. *World J Surg* 2001; **25**:718–722.

26 Omur O, Akgün A, Ozcan Z, Sen C, Ozkiliç H. Clinical implications of diffuse hepatic uptake observed in postablative and post-therapeutic I-131 scans. *Clin Nucl Med* 2009; **34**:11–14.

27 Hwang HJ, Lee SW, Kim SH. Relationship between bilirubin and C-reactive protein. *Clin Chem Lab Med* 2011; **49**:1823–1828.

28 Tomaro ML, Batlle AM. Bilirubin: its role in cytoprotection against oxidative stress. *Int J Biochem Cell Biol* 2002; **34**:216–220.

29 Kapitulnik J. Bilirubin: an endogenous product of heme degradation with both cytotoxic and cytoprotective properties. *Mol Pharmacol* 2004; **66**:773–779.

30 Onat A, Can G, Hergenc G. Serum C-reactive protein is an independent risk factor predicting cardiometabolic risk. *Metabolism* 2008; **57**:207–214.

31 Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* 2001; **286**:327–334.

32 Roy S, Banerjee U, Dasgupta A. Protective role of bilirubin against increase in hsCRP in different stages of hypothyroidism. *Indian J Clin Biochem* 2016; **31**:43–49.

33 Yu K, Kim C, Sung E, Shin H, Lee H. Association of serum total bilirubin with serum high sensitivity C-reactive protein in middle-aged men. *Korean J Fam Med* 2011; **32**:327–333.

34 Lee SG, Lee W, Kim JH, Kwon OH. Gender-specific reference intervals for serum total bilirubin in healthy Korean adults. *Clin Biochem* 2012; **45**:1257–1259.

35 Saegeman VS, Vierendeels I, Moens MJ, Moerman J. Should gender-related reference values be used for total bilirubin? *Clin Chem Lab Med* 2009; **47**:1309–1310.

36 Ganatra DA, Johar KS, Parmar TJ, Patel AR, Rajkumar S, Arora AI, *et al*. Estrogen mediated protection of cytoskeleton against oxidative stress. *Indian J Med Res* 2013; **137**:117–124.