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Excess Iodine and High-Fat Diet Combination Modulates Lipid Profile, Thyroid Hormone, and Hepatic LDLr Expression Values in Mice

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Abstract The aim of this study was to illustrate the combined effect of excess iodine and high-fat diet on lipid metabolism and its potential molecular mechanism. Sixty Balb/c mice were randomly allocated to three control groups or three excess iodine groups and fed with a high-fat diet in the absence or presence of 1,200 μg/L iodine for 1, 3, or 6 months, respectively. Serum lipid parameters and serum thyroid hormones were measured. Expressions of scavenger receptor class B type-I (SR-BI) and low density lipoproteins receptor (LDLr) mRNA and protein in liver were detected. Thyroid histology and liver type 1 iodothyronine deiodinase activity were analyzed. At the end of 3 and 6 months, compared with control, serum TC, TG, and LDL-C in excess iodine group were significantly lower ($p<0.05$). LDLr expression in liver was increased significantly ($p<0.05$) and parallel to the change of serum TC and TG. TT3 and TT4 levels in serum were elevated and TSH decreased significantly ($p<0.05$). Liver type I iodothyronine deiodinase activity was significantly higher ($p<0.05$) than control at the end of 6 months. Moreover, a time course damage effect of excess iodine combined with high-fat diet on thyroid glands was observed. The present findings demonstrated that excess iodine combined with high-fat diet could cause damage to thyroid glands and lead to thyroid hormone disorder. Those in turn caused the upregulation of hepatic LDLr gene, which resulted in the disorder in serum lipids.

Keywords Excess iodine · High-fat diet · Lipid profile · Low density lipoproteins receptor (LDLr) · Scavenger receptor class B type-I (SR-BI) · Thyroid hormone

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Introduction

Iodine is an essential trace element in thyroid physiology. Being a central constituent of the thyroid hormones, it is a key regulator of thyroid gland functions. Thyroid hormones play an important role in the regulation of metabolism and growth. According to an epidemiological survey, with rapid global progress in correcting iodine deficiency, the iodine intake of developing countries around the world has increased significantly [1–5]. In recent decades, excess iodine intake has been concerning because of its various adverse effects. It has been reported that excess iodine is not only associated with a spectrum of thyroidal effects, including hyperthyroidism, hypothyroidism, and thyroid autoimmune diseases [6–9], but that it also may cause stillbirth, abortion, embryo toxicity, and thyroid cancer [10–12]. In addition, the dose-dependent hypercholesterol effect of excess iodine has been reported in laying hens by foreign scholars [13, 14]. Our group has also found dose- and time-dependent

hypercholesterolemic effects of excess iodine on mice [15]. Moreover, the first report on the epidemiological correlation between high water iodine and dyslipidemia was published in China in 2009 [16]. Increasing evidences have suggested that excess iodine may have a potential physiological effect on lipid metabolism.

In recent decades, prevalence of dyslipidemia in China significantly increased. According to the Chinese National Nutrition and Health Survey in 2002, the prevalence of dyslipidemia in Chinese adults was 18.6% and the prevalence of hypercholesterolemia, hypertriglyceridemia, and low HDL cholesterol (HDL-C) was 2.9%, 11.9%, and 7.4%, respectively, among the participants [17]. The main reasons are rapid economic growth, higher standards of living, as well as evident trends in Western dietary pattern. In addition to high-fat diet, more and more studies have shown a potential physiological connection between excess iodine and lipid metabolism. However, the effect of excessive iodine intake combined with high-fat diet on lipid profile has not been reported and the underlying mechanisms are still elusive. Therefore, based on the previous research of our group, animal models were established in this study to investigate the time effect of excess iodine combined with high-fat diet on lipid metabolism and to explore its underlying molecular mechanisms.

Materials and Methods

Animals and Treatment

Sixty weaning female Balb/c mice (10~13 g) obtained from Sino-British Sippr/BK Lab Animal Ltd (Shanghai, China) were maintained in constant temperature-controlled rooms (22–28°C) with controlled lighting (12-h light–dark cycles) and given a commercial laboratory chow and sterile water ad libitum. The animals were cared for according to the Guiding Principles in the Care and Use of Laboratory Animals as published by the American National Institution Health. The experiments were approved by Tongji Medical College Council on Animal Care Committee. After acclimatization to the laboratory environment for 1 week, the animals were randomly divided into three control groups or three excess iodine groups (n=10) according to body weight and fed with a high-fat diet for 1, 3, and 6 months, respectively. At the same time, excess iodine groups were treated with 1,200 μg/L iodine in the form of potassium iodate (KIO_3) in the drinking water. A high-fat diet was composed of 15% lard, 10% yolk powder, and 79% standard laboratory powder chow. The content of iodine in the diet was 596 μg/kg. Data on food intake, water drink, and body weight gain of mice were recorded. At the end of 1, 3, and 6 months, the mice were made to fast for 8 h before being killed by cervical dislocation and blood was collected for serum lipid and thyroid hormones analyses. Thyroid gland was isolated for histology. Hepatic tissues were collected immediately, frozen in liquid N_2, and stored at −80°C for deiodinase activity, real-time polymerase chain reactions, and Western blot analysis.

Iodine Content

Iodine content in diet and urine was measured by modified Cer-Arsenite colorimetric method [18]. Three or two mice were placed into metabolism cages and urine samples of 3 h in the morning were collected for 3 days for urinary iodine determination.

Lipid Parameters

Concentrations of total cholesterol (TC), triglyceride (TG), LDL-cholesterol (LDL-C), and HDL-C in serum were measured by enzymatic colorimetric assay kits obtained from BIOSINO (Biotechnology and Science Inc., Beijing, China).

Real-Time Polymerase Chain Reactions

Real-time PCR was used to detect the gene expression of low density lipoproteins receptor (LDLr) and SR-BI, the key regulatory genes for lipid metabolism in liver. Total RNA from liver was extracted using TriZol (Invitrogen Life Technologies, USA) according to the manufacturers' instructions and quantified. Target mRNAs were quantified by using the SYBR green-based qRT-PCR kit (TaKaRa BIO INC, Dalian) and specific oligo primers in a real-time PCR machine (7900HT, Applied Biosystems, Forster, CA, USA). The efficiency of the PCR reactions was determined by using a series of dilutions of a standard sample. The specificity of the product was assessed by using the melting curve analyses. Gene expression levels were determined by using the $2^{-\Delta\Delta Ct}$ method. The expression values of LDLr and SR-BI were presented as fold changes relative to the control. The mRNA level of β-actin was used as an endogenous control. The forward and reverse primers were as follows: LDLr, sense primer 5′ TCA GTC CCA GGC AGC GTA T 3′, anti-sense primer 5′ CTT GAT CTT GGC GGG TGT T 3′; SR-BI, sense primer 5′ CCC AGA CAT GCT TCC CAT AA 3′, anti-sense primer 5′ GTC CGT TCC ATT TGT CCA CC 3′; β-actin, sense primer 5′ ATC GTG CGT GAC ATC AAA GA 3′, anti-sense primer 5′ ATG CCA CAG GAT TCC ATA CC 3′.

Western Blot Analysis

The liver was homogenated and lysed in RIPA lysis buffer (1% Triton X-100, 1% deoxycholate, 0.1% SDS). The

protein concentration was quantified with BIO-RAD Dc protein assay reagent (Bio-Rad, Hercules, CA, USA). Equal protein amounts were subjected to Western blot analysis. Levels of target proteins were probed with the specific primary antibodies against the target protein and the species-specific 2nd antibodies conjugated to horse-radish peroxidase. Immunoreactive bands were detected by means of an ECL plus Western Blotting Detection System (Amersham Biosciences, Little Chalford, UK) according to the manufacturer's instructions. The chemiluminescent signals were scanned from autoradiographic films (Nippon Polaroid KK, Tokyo, Japan). Quantitative analysis was performed by Gel Pro 3.0 software (Biometra, Goettingen, Germany). The antibodies used in the experiment were obtained from the following sources: purified rabbit polyclonal antibody anti-LDL receptor (ab30532) and anti-SR-BI (ab396) were purchased from Abcam Company. Mouse monoclonal anti-β-actin antibody was purchased from Sigma-Aldrich (St. Louis, MO, USA). HRP-labeled anti-rabbit IgG was obtained from Sigma company (USA).

Thyroid Hormone Concentration and Liver Type 1 Iodothyronine Deiodinase Activity Analysis

Serum total thyroxine (TT4), total triiodothyronine (TT3), and thyroid stimulating hormone (TSH) levels were measured by RIA kits obtained from the Chinese Academy of Atomic Energy (Beijing, China). The liver tissue samples for D1 activity analysis were thawed and then homogenized in a homogenization buffer (0.1 M K_2HPO_4/KH_2PO_4, 1 mM EDTA, 10 mM DTT, and 0.25 M sucrose, pH 7.0). Protein in homogenates was measured by Lowry's method [19]. D1 activity was measured by quantification of radioactive iodide released from 3′5′ [^{125}I]-rT_3. The samples were incubated for 30 min at 37°C in phosphate buffer (0.1 M K_2HPO_4/KH_2PO_4 and 1 mM EDTA, pH 6.9) with 1 nM unlabeled rT3 and 10 mM DTT. An aliquot of the supernatant containing ^{125}I, but not labeled iodothyronines, was counted in a gamma counter (Wzard-1470, Wallac).

Final enzymatic activity was expressed as picomole of I^- released per milligram of protein per minute reaction.

Thyroid Histology

Thyroid glands were placed in 10% buffered formalin, embedded in methacrylate, step-sectioned, mounted on glass slides, and stained with eosin and hematoxylin.

Statistical Methods

Data were expressed as mean ± SD and analyzed using one-way analysis of variance and Tukey's test with SPSS 12.0 software. The medians were used to describe the central tendency of urinary iodine concentration because of its skewed distribution. The Kruskal–Wallis method was used to test the differences in ranking of urinary iodine concentration. A difference of $p < 0.05$ between groups was considered as statistically significant.

Results

Average Daily Food Intake, Water Drink, and Body Weight Gain in Mice

There were no obvious differences in average daily food intake, water drink, and body weight gain among groups except that weight gain decreased significantly ($p<0.05$) at the end of 6 months with 1,200 μg/L iodine treatment (Table 1).

Urinary Iodine Content in Mice

Iodine content in urine is currently the standard biochemical marker of iodine intake [20]. Urinary iodine content in experimental mice under 1,200 ug/L iodine treatment was significantly higher ($p<0.0001$) than that of control (Fig. 1), which indicated that an animal model of excess iodine combined with high-fat diet was established successfully.

Time Course Effects of Excess Iodine Combined with High-Fat Diet on Lipid Profile

At the end of 1 month, there was no significant difference in lipid profile between excess iodine treatment and control. However, when the duration of exposure to 1,200 μg/L iodine reached 3 and 6 months, TC, TG, and LDL-C in serum were significantly lower ($p<0.05$) than those of the control. However, no significant difference was observed in HDL-C during the treatment periods (Table 2).

Time Course Effects of Excess Iodine Combined with High-Fat Diet on mRNA Abundances and Protein Content of Hepatic LDLr and SR-BIin Mice

As shown in Fig. 2, 1,200 μg/L iodine intake for 1 month did not affect mRNA and protein content in LDLr. However, upon exposure to 1,200 μg/L iodine for 3 and 6 months, LDLr mRNA and protein content were significantly higher ($p<0.05$) than those of the control. No significant changes were observed in SR-BI mRNA and protein levels during the whole experiment period (Fig. 2).

Table 1 Effect of 1,200 μg/L iodine combined with high-fat diet on food intake, water drink, and body weight gain of mice at different times

	1 month		3 months		6 months	
	HFD+0	HFD+1,200 μg/L	HFD+0	HFD+1,200 μg/L	HFD+0	HFD+1,200 μg/L
Food intake (g)	2.2±0.5	2.5±0.5	2.9±0.4	4.0±1.3	3.3±1.0	4.0±1.4
Water drink (ml)	2.9±0.5	3.3±0.4	4.5±0.9	4.6±1.2	4.5±1.4	4.9±1.1
Body weight gain (g)	9.6±1.9	8.3±2.7	14.4±2.7	13.7±2.8	19.2±2.6	14.4±1.9*

Results are expressed as means ± SD (n=10)

HFD high-fat diet

*p<0.05 (statistical significance using t-test)

Serum TT4, TT3, and TSH Concentrations and Activities of Liver Type 1 Iodothyronine Deiodinase

In high-fat diet, exposure to 1,200 μg/L iodine for 3 and 6 months resulted in abnormal thyroid hormone metabolism. It appeared that the serum levels of TT4 and TT3 were higher and TSH was significantly lower (p<0.05) than those of controls. Moreover, liver type I iodothyronine deiodinase (D1) activity of the 1200 μg/L iodine-exposed group was significantly higher (p<0.05) than those of control at the end of 6 months (Fig. 3).

Morphology of Thyroid Gland

A time course damage effect of excess iodine combined with high fat diet on thyroid glands was observed. An obvious colloid goiter and slight skin color were observed in the thyroid of mice exposed to 1,200 μg/L iodine combined with high-fat diet. As the duration of exposure was prolonged, follicular epithelial cells gradually became flattened and the follicles gradually became distended with colloid (Fig. 4).

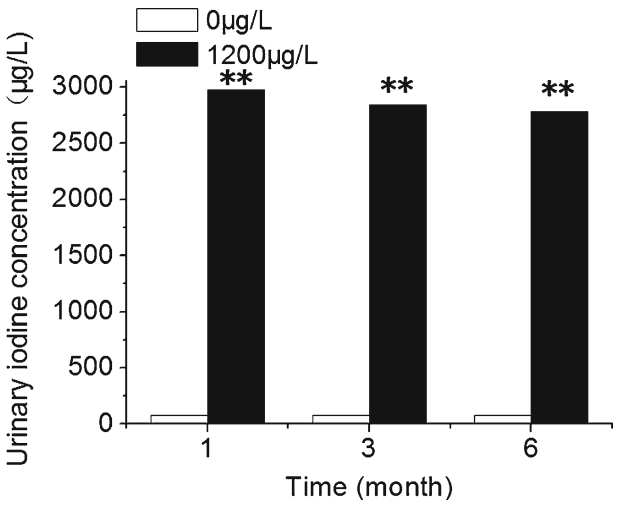

Fig. 1 Urinary iodine concentration of mice at different times. Values are medians for urinary iodine level and each *bar* represents the median of a group of seven samples. *Two asterisks* indicate that median values were significantly different from that of the control group (p<0.0001) (Kruskal–Wallis method)

Discussion

In the present study, mice were fed with high-fat diet and given drinking water containing 0 or 1,200 μg/L iodine for 1, 3, and 6 months, respectively. The results indicated that excess iodine intake combined with high-fat diet might has a significant impact on lipid profile, which was reflected by the significant decrease of serum TC, TG, and LDL-C. At exposure to excess iodine for 3 and 6 months, serum thyroid hormones TT3 and TT4 were higher than those of control and accompanied by an increased expression of hepatic LDLr mRNA and protein.

Researches have shown the hypercholesterolemic effect of excess iodine and high-fat diet alone. Thus, we thought that excess iodine combined with high-fat diet should also have a hypercholesterolemic effect on lipid profile. Interestingly, the results in this study were contrary to our expectations. In high-fat diet, excess iodine did not further elevate lipid profile but made them descend.

To further illustrate the molecular mechanisms underlying the effects of excess iodine combined with high-fat diet on lipids profile, mRNA abundances and protein content of key regulatory genes for lipid metabolism in liver were analyzed. Hepatic lipoprotein receptors including scavenger receptor class B type-I (SR-BI) and low density lipoproteins receptor are gateways of hepatic cholesterol metabolism and lipoprotein metabolism. SR-BI is a cell surface HDL receptor that mediates the selective uptake of the lipid cargo of HDL, an important process in hepatocytes, driving reverse cholesterol transport from cells in the artery wall [21]. In this study, no significant SR-BI expression was detected, suggesting that HDL-cholesterol clearance through SR-BI was not affected by excess iodine under high-fat diet pattern. This may explain the finding that concentrations of HDL-cholesterol did not change throughout the experiment.

Table 2 Time course effects of 1,200 μg/L iodine combined with high-fat diet on serum lipids

Lipids (mmol/L)	1 month		3 months		6 months	
	HFD+0	HFD+1,200 μg/L	HFD+0	HFD+1,200 μg/L	HFD+0	HFD+1,200 μg/L
TC	2.83±0.39	2.70±0.31	2.87±0.35	2.49±0.33*	2.93±0.24	2.42±0.34*
TG	1.36±0.22	1.43±0.29	1.50±0.21	1.32±0.21*	1.78±0.49	1.35±0.24*
HDL-C	1.58±0.29	1.56±0.36	1.63±0.32	1.47±0.30	1.64±0.29	1.52±0.28
LDL-C	0.61±0.11	0.62±0.10	0.75±0.14	0.55±0.12*	0.73±0.10	0.54±0.13*

Results are expressed as means ± SD (n=10)

TC total cholesterol, *TG* total triglycerides, *HDL-C* high density lipoprotein cholesterol, *LDL-C* low density lipoprotein cholesterol, *HFD* high-fat diet

*p<0.05 (statistical significance using t-test)

LDLr is a major regulator of circulating LDL-cholesterol. It is the key to maintaining the balance of cholesterol in the body. Research has shown that raising LDL receptor expression or activity can reduce blood cholesterol levels [22]. Our results also provided experimental evidence supporting such deduction and indicated that upregulation of LDLr expression may be a molecular mechanism underlying the effects of excess iodine combined with high-fat diet on lipid profile.

Expression of LDLr was regulated by several hormones. One of them is thyroid hormone [23]. Several studies have established that the effects of thyroid hormone on serum cholesterol levels are, in part, due to alterations in the expression of the hepatic LDLr [24–30]. To further illustrate the molecular mechanisms underlying the effects of excess iodine combined with high-fat diet on lipid profile, thyroid hormones were detected. The results showed that, compared with control, excess iodine intake in drinking water combined with high-fat diet significantly elevated thyroid hormone TT3 and TT4 in serum. Simultaneously, the expression of hepatic LDLr mRNA and protein increased. Our result indicated that the change in LDLr gene and

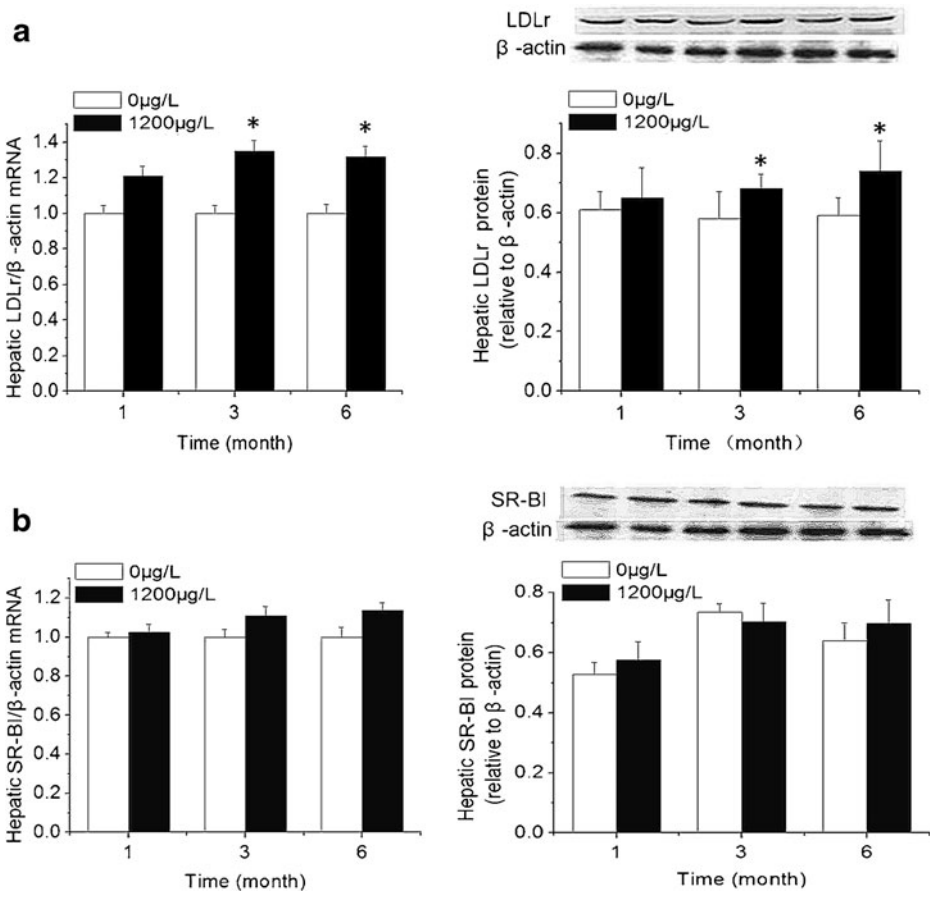

Fig. 2 Time course effects of excess iodine combined with high-fat diet on hepatic LDLr (**a**) and SR-BI (**b**) mRNA and protein expressions. Representative blots and data are expressed as means ± SD (n=3) after normalization to β-actin. Statistical analyses were performed according to ANOVA. *p<0.05 versus control

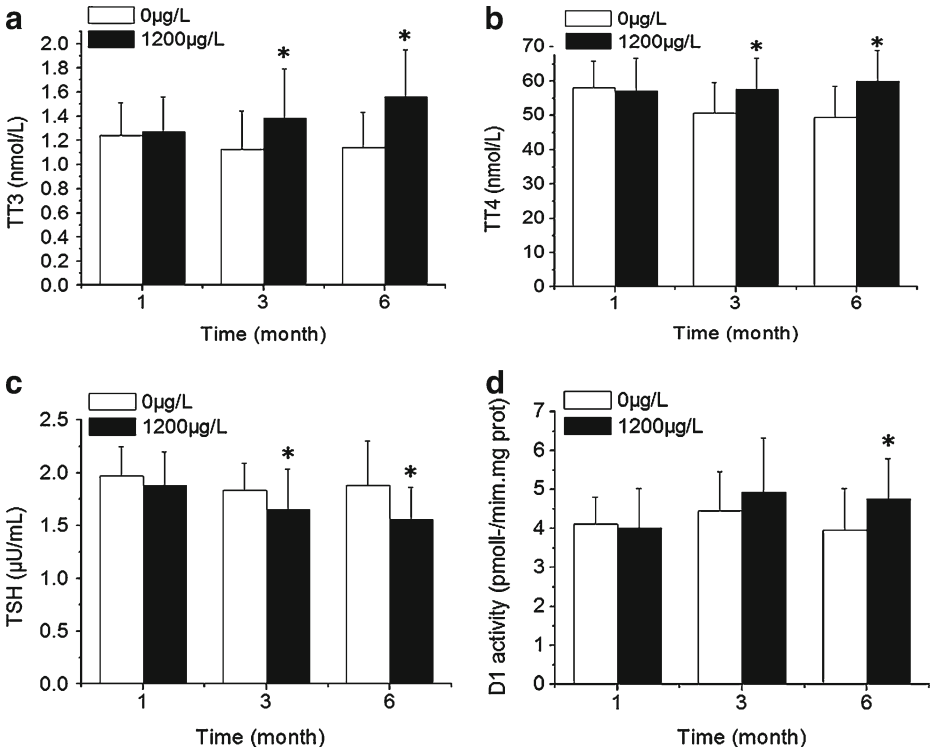

Fig. 3 Time course effects of excess iodine combined with high-fat diet on serum thyroid hormone levels and liver type 1 iodothyronine deiodinase activity in mice. Values are means for serum total triiodothyronine level (**a**), total thyroxine level (**b**), TSH level (**c**), and type 1 iodothyronine deiodinase activity (**d**) (n=10) with standard deviations represented by *vertical bars*. An *asterisk* indicates that the mean value was significantly different from that of the control group (p<0.05)

protein expression levels may be due to the variation of thyroid hormone levels in the serum.

The changes of thyroid hormone levels may be explained by follicular thyroid damage and D1 activity increase induced by excess iodine combined with high-fat diet. Thyroid follicular rupture resulted in an increase of serum TT4 and TT3, which led to a negative feedback regulation of the body and reduced the release and synthesis of TSH. Finally, the level of circulating TSH decreased. In our previous study, no changes of serum TT4, TT3, and TSH were observed in mice given normal feed and excess iodine [15]. However, the present study showed that excess iodine combined with high-fat diet not only increased the damage of thyroid but also led to hormone disturbance. Therefore, our result demonstrated that excess iodine combined with high-fat diet has a more seriously damaging effect on thyroid gland than excess iodine alone. In addition, our research showed that the changes in liver type I iodothyronine deiodinase activity and serum TT3 concentration were consistent. It has been reported that excess iodine impairs thyroid hormone

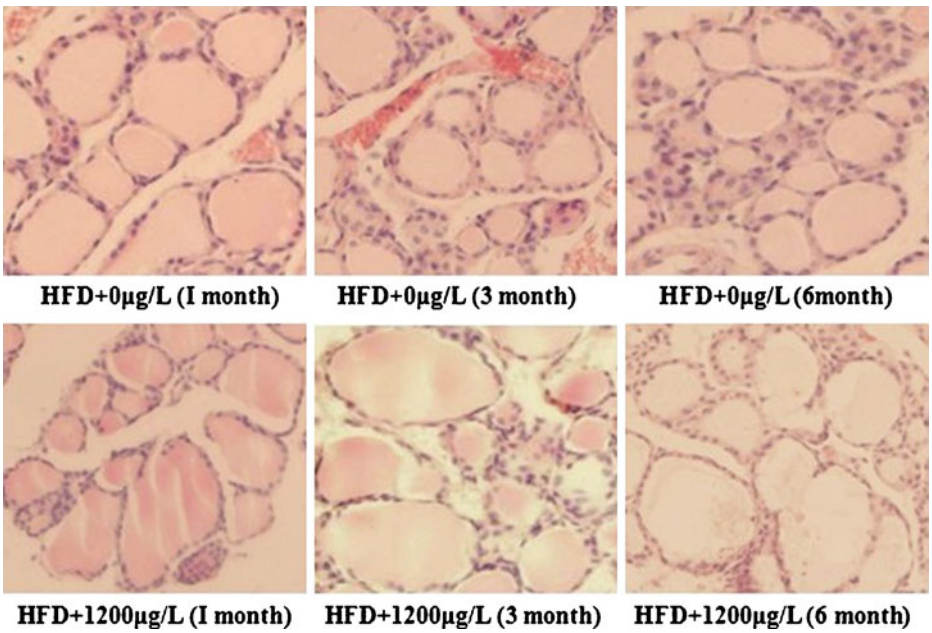

Fig. 4 Effect of 1,200 μg/L iodine combined with high-fat diet on histology changes of thyroid at different times (H&E, magnification×100). *HFD* high fat diet

secretion and metabolism mainly through affecting iodothyronine deiodinase activity [31, 32]. The primary role of iodothyronine deiodinase is catalytic deiodination of TT4 in peripheral tissues to provide cycle TT3, which plays an important role in the regulation of thyroid hormone [33]. These conclusions were consistent with our result. However, the mechanism involved in the interaction of thyroid hormone and D1 activity needs to be studied further.

In conclusion, the present findings demonstrated that excess iodine combined with high-fat diet could cause damage to the thyroid glands and could lead to thyroid hormone disorder. Those in turn caused the upregulation of hepatic LDLr gene, which resulted in the disorder in serum lipids. Meanwhile, our result demonstrated that excess iodine combined with high-fat diet has a more seriously damaging effect on thyroid gland than excess iodine alone. Therefore, in high-fat diet, excess iodine intake should be monitored to make sure that it is within optimum levels for health.

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