Biol Trace Elem Res (2015) 168:447–452
DOI 10.1007/s12011-015-0371-y

Effects of 3,5-Diiodotyrosine and Potassium Iodide on Thyroid Function and Oxidative Stress in Iodine-Excess Wistar Rats

Dan Liu[1] · Xinying Lin[1] · Fugui Yu[2] · Man Zhang[1] · Hongxia Chen[3] · Wei Bao[4] · Xia Wang[5]

Received: 21 December 2014 / Accepted: 13 May 2015 / Published online: 24 May 2015

Abstract The objective of this study was to investigate the effects of organic iodine (3,5-diiodotyrosine, DIT) and inorganic iodine (potassium iodine, KI) on thyroid function and oxidative stress in iodine-excess Wistar rats. Seventy-two Wistar rats were randomly divided into eight groups: normal control (NC), thyroid tablet-induced hyperthyroidism model (HM), low DIT (L-DIT), medium DIT (M-DIT), high DIT (H-DIT), low KI (L-KI), medium KI (M-KI), and high KI (H-KI). All rats were fed ad libitum for 30 days. Morphological changes in the thyroid, absolute and relative weights of the thyroid, thyroid function markers free triiodothyronine (FT3) and free thyroxine (FT4), urinary iodine level, and oxidative stress indicators were measured. Compared to the HM groups, the FT3 and FT4 levels decreased in the L-DIT groups; the thyroid weight and thyroid weight/body weight values decreased markedly in the L-DIT and M-DIT groups; serum superoxide dismutase/malondialdehyde increased markedly; glutathione peroxidase activity increased markedly in the L-DIT groups; and malondialdehyde levels decreased significantly in the M-DIT groups. However, the FT3 and FT4 levels decreased and glutathione peroxidase levels increased significantly in the DIT groups compared to their corresponding KI groups. Additionally, urinary iodine levels increased significantly in both DIT and KI groups, while the highest urinary iodine excretion was showed in the DIT groups among groups. When the addition of iodine with the same doses in iodine-excess rats, although neither DIT nor KI normalized iodine levels in the iodine-excess rats, the DIT did less damage than did KI to thyroid follicular cells. Therefore, DIT rather than KI had a protective effect by balancing the antioxidant system when exposed to supraphysiological iodine. These suggest that DIT may be used as a new alternative iodized salt in the universal salt iodization to avoid the potential damage of surplus KI.

Keywords Potassium iodide · 3,5-diiodotyrosine · Hyperthyroidism thyroid

✉ Xinying Lin
xinyingll@sdu.edu.cn

✉ Xia Wang
wangxiaes@sdu.edu.cn

[1] Department of Nutrition and Food Hygiene, School of Public Health, Shandong University, 44 Wenhuaxi Road, Jinan 250012, People's Republic of China

[2] Shandong food and drug administration, Jinan, Shandong, China

[3] Institution of Biomedicine, Taihe Hospital, Hubei University of Medicine, Shiyan, Hubei, China

[4] Department of Nutrition and Food Hygiene, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

[5] Department of Maternal and Child Health Care, School of Public Health, Shandong University, 44 Wenhuaxi Road, Jinan 250012, People's Republic of China

Introduction

Iodine, which is the structural component of thyroid hormones, plays an important role in development, metabolism, thermoregulation, and growth [1]. Since the implementation of the universal salt iodization policy in many nations over the last several decades, iodine deficiency has fundamentally improved worldwide [2]. However, hyperthyroidism remains a concern, and there is little consensus regarding the mechanisms. Previous studies reported that both high and low iodine intakes could lead to hyperthyroidism [3–5], indicating a need for dietary adjustments. This study, therefore, aimed to

elucidate the effects and potential mechanisms of excess iodine exposure.

Iodine has been demonstrated to have an antioxidant effect in thyroids and other tissues [6]. Moreover, iodine also seems to be related to the activity of the glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD) [7]. There are two forms of iodine, organic and inorganic iodine, in the organism [8]. Common inorganic iodine includes potassium iodine (KI) and potassium iodate, and common organic iodine includes monoiodotyrosine (MIT) and 3,5-diiodotyrosine (DIT) (Fig. 1). Some studies have shown that DIT, which is a kind of tyrosine derivatives, has a unique advantage at the daily dose, and it modifies some parameters of the oxidation kinetic without side effects [9]. Moreover, the antioxidant effect of organic iodine may be better than that of inorganic iodine [10]. We speculate that DIT's scavenging effect on reactive oxygen species may be stronger. Thus, in this study, we also explore the relationship between high iodine and thyroid function as well as the potential curable value of DIT in the iodine-excess rat model.

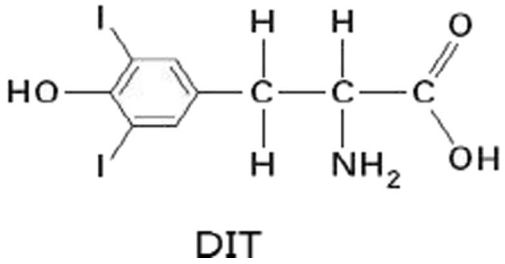

Fig. 1 The chemical structure of 3,5-diiodotyrosine (DIT)

Materials and Methods

Animal Treatment

All experimental protocols were approved by the Institutional Animal Ethics Committee, and all procedures were performed in accordance with ethical standards. Animals were maintained at 25±2 °C under standard conditions in animal room of Shandong University. Male Wistar rats with a body weight (BW) of 190–210 g were obtained from the Experimental Animal Center of Shandong University. They were randomly assigned to the following eight treatment groups: normal control (NC), thyroid tablet-induced hyperthyroidism model (HM), low DIT (L-DIT), medium DIT (M-DIT), high DIT (H-DIT), low KI (L-KI), medium KI (M-KI), and high KI (H-KI). NC group was treated with saline solution; HM group was treated with thyroid tablets at the dosage of 200 mg/kg.BW by oral administration. Low, medium, and high doses of DIT and KI were 25, 166.7, and 500.1 μg iodine/kg.BW, respectively. The DIT and KI groups were treated with different doses of DIT or KI and co-treated with the thyroid tablets.

The recommended nutrient intakes of 150 μg/day and tolerable upper intake level of 1000 μg/day (equivalent to approximately 2.5 and 16.7 μg/kg.BW, respectively) for adults meet needs and prevent excess intake [11, 12]. In this study, the low, medium, and high doses of iodine were set at 25, 166.7, and 500.1 μg iodine/kg.BW, respectively, which is 10 times of recommended nutrient intakes and 10 times and 30 times of upper intake level.

The thyroid tablets (Yanzhou Shengbao Pharmaceutical Co., LTD) contained the skimmed dry thyroid tissues, which can promote metabolism, growth, and development. The main components of the thyroid tablet were thyroxine and thyroid original three iodine glycine. The concentration of the thyroid tablet suspension was 40 mg/ml. Thyroid tablets and KI (AR, Shandong Chemical Research Institute) were used to induce hyperthyroidism in our model, as described in previous studies [13–15]. DIT was extracted from kelp by our laboratory, and its concentration was 20,000 mg/kg.

After a 30-day administration, the rats were sacrificed under anesthesia. Blood samples were collected and stored. Body weight and wet organ weight were measured. The thyroid relative weight was calculated by the wet thyroid weight (mg) divided by body weight (100 g). The cellular morphology of thyroid stained with routine Hematoxylin and Eosin (HE) was observed with an optical microscope.

Measurements of Biomarkers

Serum free triiodothyronine (FT3) and serum free thyroxine (FT4) were measured using commercial kits (Beijing Kemeidongya Bioengineering Institute, China). SOD, GSH-Px, and malondialdehyde (MDA) levels were also measured using commercial kits (Nanjing Jiancheng Bioengineering Institute, China). Urinary iodine was analyzed by arsenic cerium catalysis spectrophotometry (Standards of the People's Republic of China on Health Industry).

Statistical Analysis

Data were expressed as mean±standard deviation (mean±SD) and analyzed using SAS software. Analysis of variance was used for comparison of more than two groups, and T test was used for comparison of two group means. A $P<0.05$ was considered statistically significant.

Results

General Condition

The main symptoms of all experimental groups including agitation, difficulty in oral administration, and increased appetite were observed except the NC group. The feces and urine were

not abnormal. Compared with the NC group, the body weight of the experimental groups decreased significantly by the end of the experiment. Compared with the HM group, the body weight increased significantly in the M-DIT and H-DIT groups. The body weight increased markedly in the M-DIT and H-DIT groups, compared DIT groups to the corresponding KI groups.

Changes in Thyroid Function and Weight Induced by Excess Iodine

The FT3 and FT4 levels, body weight, and relative weight of the thyroid in each group are shown in Table 1. There was a significant difference between the NC group and the other groups. In other seven groups, body weights decreased and serum FT3 and FT4 levels increased. There was an increase in the thyroid weight/body weight (TW/BW) ratio in the HM, M-KI, and H-KI groups. Compared with the HM group, the thyroid weight and TW/BW ratio decreased in the L-DIT and M-DIT groups, and serum FT3 and FT4 levels decreased significantly in the L-DIT group. Compared to their corresponding KI groups, serum FT3 and FT4 levels decreased significantly in the DIT groups, and the thyroid weight and TW/BW ratio decreased in the H-DIT groups.

Changes in Urinary Iodine Induced by Excess Iodine

The urinary iodine levels of each group are given in Table 2. Compared with the NC and HM groups, respectively, the DIT and KI groups showed a significant rise in terms of urinary iodine levels. In addition, the urinary iodine levels of the DIT groups were higher than those of their corresponding KI groups. The M-DIT and H-DIT groups achieved statistical significance.

Changes in Oxidative Stress Indicators Induced by Excess Iodine

A comparison of serum SOD and GSH-Px activity and MDA and SOD/MDA values can be seen in Table 3. Compared with the NC groups, the HM groups showed elevated MDA levels and decreased SOD, GSH-Px, and SOD/MDA levels. By comparison with the HM groups, the MDA levels was decreased in the M-DIT groups, GSH-Px activity increased in L-DIT groups, and the SOD/MDA levels increased significantly in the DIT groups. Compared to their corresponding KI groups, the GSH-Px and SOD/MDA levels increased significantly in the DIT groups.

Changes in Cell Morphology Induced by Excess Iodine

The thyroid morphology and quantitative observation under an optical microscope are shown in Fig. 2. The follicular cells of the thyroid in the HM groups had great variability in size, and the cell colloid decreased and even disappeared. Cell abnormalities can be seen in follicular cavities. In the KI groups, the degree of pathological change in the thyroid follicles had a dose-effect relation, with the impairment aggravating gradually as the dosage increased. In the H-DIT groups, the degree of lesions was similar to that of the HM groups, but the L-KI and M-KI groups had only slight pathological changes.

Discussion

This present study suggested that supraphysiological iodine exposure could induce hyperthyroidism. DIT protected against hyperthyroidism and had a positive effect on thyroid function by attenuating oxidative stress. Compared with KI, DIT's scavenging effect on reactive oxygen species was stronger.

Table 1 Effect of different treatments on free T3 and T4 levels (picomole per liter), body weight (g) and thyroid weight (mg), and TW/BW (thyroid weight/body weight) in different groups (Mean±SD)

Group	Iodine dosage (μg/kg)	Number (*n*)	FT3 (pmol/L)	FT4 (pmol/L)	Body weight (g)	Thyroid weight (mg)	TW/BW (mg/100 g)
NC	–	8	5.08±2.61	2.98±1.52	272.11±10.67	29.70±4.66	9.64±1.82
HM	–	9	26.11±11.09▲▲	11.48±3.77▲▲	237.47±15.55▲▲	34.12±7.52	12.97±1.66▲▲
L-DIT	25	9	17.34±2.64▲▲ ■★★	7.10±1.91▲▲ ■★★	252.21±12.13▲▲	26.57±3.01■	9.98±1.08■■
M-DIT	166.7	9	17.68±4.72▲▲★★	7.67±3.20▲▲★	261.24±14.66■★★	27.09±4.66■	10.34±2.48■
H-DIT	500.1	8	19.97±2.25▲▲★	8.02±2.57▲▲★	258.36±11.41▲ ■★★	28.28±5.30★	10.93±2.37★
L-KI	25	9	24.06±5.35▲▲	10.76±2.33▲▲	252.20±10.04▲▲	27.42±4.21	11.71±2.77
M-KI	166.7	9	26.91±7.80▲▲	10.82±2.20▲▲	238.47±16.06▲▲	31.59±6.73	12.53±2.92▲
H-KI	500.1	9	29.88±12.65▲▲	11.05±2.75▲▲	235.38±14.48▲▲	34.18±5.49	13.61±2.08▲▲

▲ $P<0.05$, ▲▲ $P<0.01$ (vs. NC); ■ $P<0.05$, ■■ $P<0.01$ (vs. HM); ★ $P<0.05$, ★★ $P<0.01$ (DIT vs. KI)

Table 2 Rat urine iodine (microgram per liter) in different groups (Mean±SD)

Group	Iodine dosage (μg/kg)	Number (*n*)	Urine iodine (μg/L)
NC	–	8	58.64±35.50
HM	–	9	539.80±162.48▲▲
L-DIT	25	9	1844.33±292.74▲▲▪
M-DIT	166.7	9	4222.33±299.74▲▲▪★★
H-DIT	500.1	8	4092.00±306.23▲▲▪★★
L-KI	25	9	1763.39±185.35▲▲▪▪
M-KI	166.7	9	2510.89±182.75▲▲▪▪
H-KI	500.1	9	2770.75±188.43▲▲▪▪

▲ $P<0.05$, ▲▲ $P<0.01$ (vs. NC); ▪ $P<0.05$, ▪▪ $P<0.01$ (vs. HM); ★ $P<0.05$, ★★ $P<0.01$ (DIT vs. KI)

DIT is found in seaweed and kelp of the genus Laminaria. Figure 1 shows the chemical structure of DIT. Thyroid cells, under the stimulus of thyroid stimulating hormone, delivered the iodine ion into follicle cells through sodium-potassium pump, and then, it was oxidized to iodine molecules rapidly. Iodine molecules combine with tyrosine could produce MIT and DIT in thyroglobulin. Two DIT coupling formed thyroxine, and MIT combined with DIT formed triiodothyronine.

In the present study, compared with the HM groups, the serum FT3 and FT4 levels decreased significantly in the L-DIT groups, body weights increased in the M-DIT and H-DIT groups, and thyroid weight and TW/BW decreased in the L-DIT and M-DIT groups. Moreover, compared to their corresponding KI groups, the serum FT3 and FT4 levels obviously declined, and the thyroid weight and TW/BW ratio decreased in the H-DIT groups. These findings suggested that DIT could protect against hyperthyroidism, which were consistent with other studies' results [16, 17].

As one of tyrosine derivatives, DIT had the similar physiological function to tyrosine. Previous studies had shown that high tyrosine could relieve the symptom of hyperthyroidism and restore the deformed cell morphology of the thyroid gland [18]. As shown in Fig. 2, the damage in thyroid was visible under light microscopy in the HM groups. In the experimental groups, the DIT groups experienced milder pathological changes than did the KI groups at the same dose levels. This difference might be related to the Wolff-Chaikoff effect [19]. Iodine organification was restrained, in response to the increasing iodide intakes, leading to a high concentration of inorganic iodide within thyroid cells. Whereas inorganic iodine could affect the thyroid function and damage the follicular cells morphology, organic iodine may be not or less.

Rats under the hyperthyroidism condition were administrated high iodine. The vast majority of iodine was not absorbed because of feeble demand, and thus, they excreted in the urine after kidney metabolism. Compared with the NC groups, the three DIT and KI groups showed a significant rise in urinary iodine levels. In addition, the urinary iodine levels of the DIT groups were higher than those of the corresponding KI groups. That difference might be caused by the two different forms of iodine, organic iodine in the DIT groups and inorganic iodine in the KI groups, which resulted in different absorption and metabolic processes and different renal elimination rates. Some studies reported that redundant organic iodine in the excretory system can prevent the high-iodine goiters [20, 21]. However, further research is needed to confirm this finding.

Growing evidences suggested that patients with hyperthyroidism were subject to oxidative stress and that hyperthyroidism was associated with an increase in free radical production [22, 23], leading to a large number of lipid peroxides appeared in the thyroid gland. In this study, rats with hyperthyroidism were supplemented with DIT or KI for 30 days. Our data showed an elevation in MDA levels and a decline in SOD, GSH-Px, and SOD/MDA levels, compared with the NC groups. These findings suggested that hyperthyroidism was characterized by increased oxidative stress and increased free radicals. By comparison with the HM groups, the MDA levels decreased significantly in the M-DIT groups, GSH-Px activity

Table 3 Effect of different treatments on serum SOD activity (units per milliliter), MDA content (nanomole per milliliter), GSH-Px activity (units) and SOD/MDA value in different groups (Mean±SD)

Group	Iodine dosage (μg/kg)	Number (*n*)	SOD (U/ml)	MDA (nmol/ml)	SOD/MDA	GSH-Px (U)
NC	–	8	231.70±13.83	6.40±2.86	41.01±12.71	766.68±93.98
HM	–	9	213.28±15.24▲	9.78±1.12▲	22.10±3.3▲▲	655.73±87.46▲
L-DIT	25	9	220.84±26.5	7.47±2.64	32.55±12.06▪	758.21±92.40▪★
M-DIT	166.7	9	203.25±13.93▲▲	7.22±3.14▪	30.47±9.19▪	736.27±108.39★
H-DIT	500.1	8	208.26±29.00	7.68±2.05	29.98±6.19▲▪	726.05±118.89★
L-KI	25	9	216.62±8.00▲	7.90±2.86	28.72±9.35▲	637.66±140.20▲
M-KI	166.7	9	204.15±14.78▲▲	8.87±2.25	25.81±6.38▲▲	608.86±138.92▲
H-KI	500.1	9	187.67±43.73▲	8.30±2.62	23.77±7.19▲▲	591.06±116.55▲▲

▲ $P<0.05$, ▲▲ $P<0.01$ (vs. NC); ▪ $P<0.05$, ▪▪ $P<0.01$ (vs. HM); ★ $P<0.05$, ★★ $P<0.01$ (DIT vs. KI)

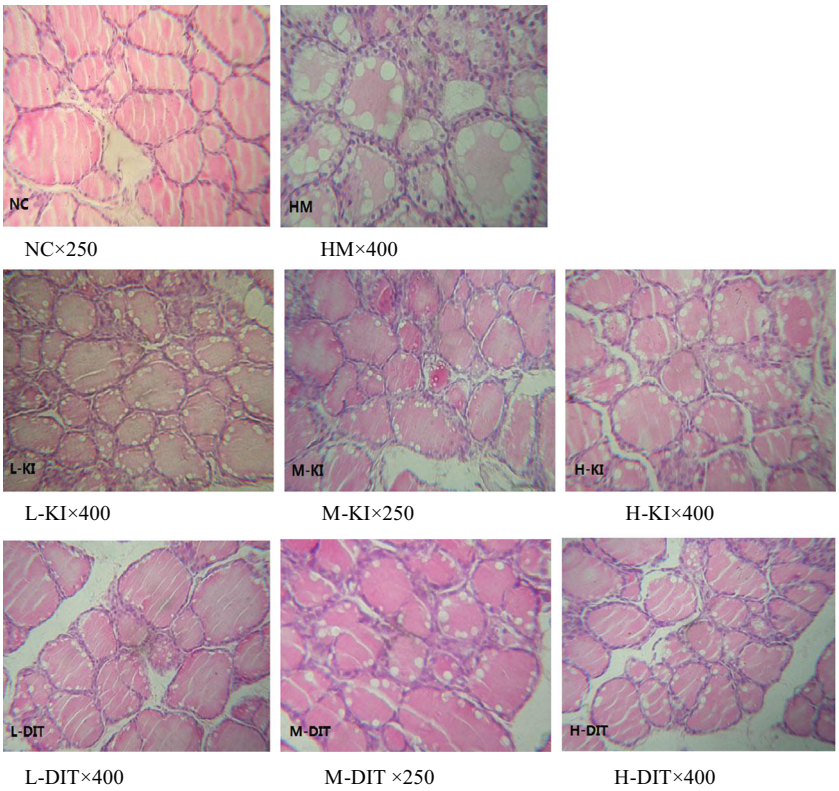

Fig. 2 Thyroid morphological changes under optical microscope (H & E staining, ×400 or ×250)

increased in the L-DIT groups, and the SOD/MDA levels increased significantly in the DIT groups. Compared to their corresponding KI groups, GSH-Px activity increased significantly in the DIT groups.

These findings had different implications. On the one hand, in addition to being a component of the thyroid hormone, iodine could act as an antioxidant that helped to maintain the integrity of several organs [24]. Moreover, the antioxidant effect of molecular iodine was better than that of ionic iodine. Molecular iodine exerted a 50-fold greater antioxidant action than did KI [10]. However, another study showed that iodine, especially organic iodides, might be a risk factor for thyroid hypertrophy, although the mechanism involved in this toxicity was unclear [25]. Iodine, especially organic iodine, probably had important implications, but further research on oxidative stress mechanism is needed for hyperthyroidism.

This study proved that DIT had certain strengths on antioxidant status. Thus, we suggested that the DIT's antioxidant effect on reactive oxygen species might be better than KI. The mechanism might be related to the chemical structure of DIT, which carries a phenolic hydroxyl unit that can provide the proton to block free radical reaction. There were, however, several limitations of this study. We did not measure the thyroid-stimulating hormone levels. We also did not use a Lugol solution and iodine oil to compare with the DIT results. And other antioxidants, such as vitamin C, should be compared in the following experiments. Furthermore, the antioxidant mechanisms of DIT were unclear, and more experiments were needed to investigate the role of organic iodine in antioxidant status.

In conclusion, this study suggested that DIT as an organic iodine source might be a safer and more effective method of iodine supplementation than inorganic iodine. DIT probably was regarded as a new alternative way of iodized salt in the universal salt iodization, which at present usually used inorganic iodine such as KI.

Acknowledgments This work was sponsored by the Health Department of Shandong Province, China (no. 2001CA1AA18) and National Natural Science Foundation (NSFC 81370966) of China.

Conflict of Interest The authors declare that they have no competing interests.

Glossary

KI	Potassium iodine
DIT	3,5-diiodotyrosine
GSH-Px	Glutathione peroxidase
SOD	Superoxide dismutase
MDA	Malondialdehyde
FT3	Free triiodothyronine
FT4	Free thyroxine

References

1. Vanderpump M (2014) Thyroid and iodine nutritional status: a UK perspective. Clin Med 14(Suppl 6):s7–s11. doi:10.7861/clinmedicine.14-6-s7
2. Delange F, Lecomte P (2000) Iodine supplementation: benefits outweigh risks. Drug Saf 22:89–95
3. Leung AM, Braverman LE (2014) Consequences of excess iodine. Nat Rev Endocrinol 10:136–142. doi:10.1038/nrendo.2013.251
4. Garcia-Fuentes E, Gallo M, Garcia L et al (2008) Amniotic fluid iodine concentrations do not vary in pregnant women with varying iodine intake. Br J Nutr 99:1178–1181. doi:10.1017/s00071145078 62398
5. Konno N, Yuri K, Taguchi H, Miura K et al (1993) Screening for thyroid diseases in an iodine sufficient area with sensitive thyrotrophin assays, and serum thyroid autoantibody and urinary iodide determinations. Clin Endocrinol (Oxf) 38:273–281
6. Smyth PP (2003) Role of iodine in antioxidant defence in thyroid and breast disease. Biofactors 19(3–4):121–130
7. Soriguer F, Gutierrez-Repiso C, Rubio-Martin E et al (2011) Iodine intakes of 100–300 mug/d do not modify thyroid function and have modest anti-inflammatory effects. Br J Nutr 105(12):1783–1790. doi:10.1017/s0007114510005568
8. Kupper FC, Carpenter LJ, Leblanc C et al (2013) In vivo speciation studies and antioxidant properties of bromine in Laminaria digitata reinforce the significance of iodine accumulation for kelps. J Exp Bot 64(10):2653–2664. doi:10.1093/jxb/ert110
9. Doerge DR, Taurog A, Dorris ML (1994) Evidence for a radical mechanism in peroxidase-catalyzed coupling. II. Single turnover experiments with horseradish peroxidase. Arch Biochem Biophys 315(1):90–99. doi:10.1006/abbi.1994.1475
10. Aceves C, Anguiano B, Delgado G (2013) The extrathyronine actions of iodine as antioxidant, apoptotic, and differentiation factor in various tissues. Thyroid 23(23):938–946. doi:10.1089/thy.2012.0579
11. Fisher DA, Oddie TH (1969) Thyroidal radioiodine clearance and thyroid iodine accumulation: contrast between random daily variation and population data. J Clin Endocrinol Metab 29:111–115. doi:10.1210/jcem-29-1-111
12. Trumbo PR (2013) Evidence needed to inform the next dietary reference intakes for iodine. Adv Nutr 4:718–722. doi:10.3945/an.113.004804
13. Subudhi U, Das K, Paital B et al (2008) Alleviation of enhanced oxidative stress and oxygen consumption of L-thyroxine induced hyperthyroid rat liver mitochondria by vitamin E and curcumin. Chem Biol Interact 173:105–114. doi:10.1016/j.cbi.2008.02.005
14. Kumar N, Kar A, Panda S (2014) Pyrroloquinoline quinone ameliorates l-thyroxine-induced hyperthyroidism and associated problems in rats. Cell Biochem Funct 32:538–546. doi:10.1002/cbf.3048
15. Xia Y, Qu W, Zhao LN et al (2013) Iodine excess induces hepatic steatosis through disturbance of thyroid hormone metabolism involving oxidative stress in BALB/c mice. Biol Trace Elem Res 154:103–110. doi:10.1007/s12011-013-9705-9
16. Ladenson PW, Kieffer JD, Farwell AP et al (1986) Modulation of myocardial L-triiodothyronine receptors in normal, hypothyroid, and hyperthyroid rats. Metabolism 35:5–12
17. Araujo AS, Ribeiro MF, Enzveiler A et al (2006) Myocardial antioxidant enzyme activities and concentration and glutathione metabolism in experimental hyperthyroidism. Mol Cell Endocrinol 249:133–139. doi:10.1016/j.mce.2006.02.005
18. Carter WJ, Benjamin WS, Faas FH (1982) Effects of experimental hyperthyroidism on protein turnover in skeletal and cardiac muscle as measured by [14C]tyrosine infusion. Biochem J 204:69–74
19. De La Vieja A, Dohan O, Levy O et al (2000) Molecular analysis of the sodium/iodide symporter: impact on thyroid and extrathyroid pathophysiology. Physiol Rev 80(3):1083–1105
20. Mostbeck A, Galvan G, Bauer P et al (1998) The incidence of hyperthyroidism in Austria from 1987 to 1995 before and after an increase in salt iodization in 1990. Eur J Nucl Med 25(4):367–374
21. Gao T, Shi R, Qi T et al (2014) A comparative study on the effects of excess iodine and herbs with excess iodine on thyroid oxidative stress in iodine-deficient rats. Biol Trace Elem Res 157:130–137. doi:10.1007/s12011-013-9873-7
22. Joanta AE, Filip A, Clichici S et al (2006) Iodide excess exerts oxidative stress in some target tissues of the thyroid hormones. Acta Physiol Hung 93:347–359. doi:10.1556/APhysiol.93.2006.4.11
23. Fernandez V, Barrientos X, Kipreos K et al (1985) Superoxide radical generation, NADPH oxidase activity, and cytochrome P-450 content of rat liver microsomal fractions in an experimental hyperthyroid state: relation to lipid peroxidation. Endocrinology 117:496–501. doi:10.1210/endo- 117-2-496
24. Gutierrez-Repiso C, Velasco I, Garcia-Escobar E et al (2014) Does dietary iodine regulate oxidative stress and adiponectin levels in human breast milk? Antioxid Redox Signal 20(5):847–853. doi:10.1089/ars.2013.5554
25. Glatt CM, Ouyang M, Welsh W et al (2005) Molecular characterization of thyroid toxicity: anchoring gene expression profiles to biochemical and pathologic end points. Environ Health Perspect 113(10):1354–1361