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The Impact of Dietary Iodine Intake on Lipid Metabolism in Mice

Shu-Jun Zhao · Yan Ye · Fu-Jun Sun · En-Jiang Tian · Zu-Pei Chen

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Abstract The present study has been designed to investigate the impact of dietary iodine intake on lipid metabolism in mice, including iodine deficiency and iodine excess. Different amounts of iodine mixed in the drinking water were continuously administered to mice. The body weights and the levels of urinary iodine were measured 8 months after the treatment. Thyroid hormones in the serum were detected by chemiluminescence immunoassay. Serum total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol and low-density lipoprotein cholesterol (LDL-C) were determined enzymatically by automatic analyzer. Results showed that the urine iodine concentrations paralleled the amounts of iodine intakes. No statistical differences of body weights among different groups were found. The levels of thyroid hormones were dramatically decreased in iodine deficiency while no significant differences were found between iodine excess groups and normal iodine group. In iodine deficiency groups, the levels of TG, TC, and LDL were increased at varying degrees. In iodine excess groups, the levels of TG in the male mice and the levels of TC in the female mice were much lower than normal iodine group. In conclusion, dietary iodine intake may affect the metabolism of serum lipids. Hypothyroid function induced by iodine deficiency may be responsible for the changes of lipids. Higher iodine intake might benefit lipid metabolism.

Keywords Iodine intake · Lipid metabolism · Total cholesterol triglyceride · High-density lipoprotein cholesterol · Low-density lipoprotein cholesterol · Thyroid hormones

Introduction

In recent years, a relationship between dietary salt intake and blood pressure has been discovered. Sodium restriction is of importance for reducing hypertension and the risk of cardiovascular disease. A recent meta-analysis reviewed randomized studies examining the effects of a low-sodium vs high-sodium diet in normotensive individuals [1]. A small but significant decrease in systolic and diastolic blood pressure was observed; however, there was a

S.-J. Zhao (✉) · Y. Ye · F.-J. Sun · E.-J. Tian · Z.-P. Chen
Institute of Endocrinology, Tianjin Medical University, Tianjin, China
e-mail: zhaoshj@tijmu.edu.cn

simultaneous and significant increase in plasma lipids. Concerning concomitant changes in iodine intake might happen during sodium (iodized salt) restriction, it may be deduced that the amount of iodine intake would have some influence on the lipid metabolism. Some data have shown a declining trend in iodine intake. For instance, the proportion of the US population with moderate to severe iodine deficiency (<50 μg iodine/L in urine) has more than quadrupled in the last 20 years, 2.6% in NHANES (National Health and Nutrition Examination) I vs 11.7% in NHANES III (NHANES I, 1971–74 and NHANES III, 1988–94) [2]. Comparable trends have also been observed in other countries that use iodize salt [3]. Although sodium restriction may improve physiological variables such as blood pressure, the adverse effects of concomitantly reduced iodine intake (in regions where salt is iodized) over the long-term are unknown. In this study, based on the successful establishment of animal models, the impact of dietary iodine intake on lipid metabolism was explored.

Materials and Methods

Animals

Balb/c mice (4–6 weeks), weighing about 16 g, half males and half females, were randomly divided into five groups (for each group, n=20), including group 1: severe iodine deficiency (SID); group 2: mild iodine deficiency (MID); group 3: normal iodine (NI); group 4: 10-fold high iodine (10 HI), and group 5: 50-fold high iodine (50 HI). They were acclimatized in animal house and were exposed to normal cycles of day and night and free to drink water.

Assessment of Urine Iodine Concentration

Urine iodine concentration was determined by As^{3+}-Ce^{4+} catalytic spectrophotometry using ammonium persulfate digestion method [4].

Determination of the Body Weights

Electronic balance was used to determine the body weights of the mice.

Estimation of Serum Lipids Concentrations

Serum total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were measured by enzymatic colorimetric test kits purchased from BioSino Bio-technology and Science Inc.

Estimation of Serum Thyroid Hormones Concentrations

The serum concentrations of total thyroxine (TT_4), total triiodothyronine (TT_3), free thyroxine (FT_4), and free triiodothyronine (FT_3) were determined by the chemiluminescence immunoassay kit (Roche Diagnostic, (Shanghai) Ltd).

Experimental Protocols

After 2 weeks adaptation to standard chow diet and tap water, all the mice in the five groups were fed with low-iodine forage of the foodstuff obtained from an endemic goiter area (per kilo

forge containing 30% soybean, 40% corn, 20% wheat, 10% millet, 3 g methionine, 1 g lysine, inorganic salts, and vitamins according to the "Laboratory animals—Mice and rats formula feeds, GB 14924.3"; average iodine content in diet is 20–50 μg/kg) and drank deionic water containing different concentrations of potassium iodide. The iodine content in water was 0, 196.08, 326.79, 3,856.21, and 19,542.5 μg/L, respectively. Eight months after administration, metabolic cages were used to collect the urine of the mice from each group. Blood samples were obtained after sacrificing the animals and stored at −70°C until analysis.

Statistical Analysis

SPSS was used to analyze the collected data. Data for urine iodine concentration were expressed as median and statistically analyzed by using rank sum test. Data for body weights, serum lipids concentrations, and serum thyroid hormones concentrations were expressed as mean ± SD and statistically analyzed by using one-way ANOVA followed by a Fisher test. LSD or Dunnett's T3 post hoc test was used when it was appropriate. A p value less than 0.05 was considered statistically significant.

Results

Determination of Urine Iodine Concentration in Each Group

Median urinary iodine concentrations in NI, SID, MID, 10 HI, and 50 HI group were 233.8, 7.2, 155.7, 4,950.9, and 28,900.7 μg/L, respectively. Compared with NI group, urine iodine concentrations were much lower in both iodine deficiency groups especially in SID group and much higher in iodine excess groups. The urine iodine concentrations paralleled the amounts of iodine intakes.

Determination of the Body Weights

There were no statistical differences of body weights among the same gender mice from different iodine intake groups (Figs. 1).

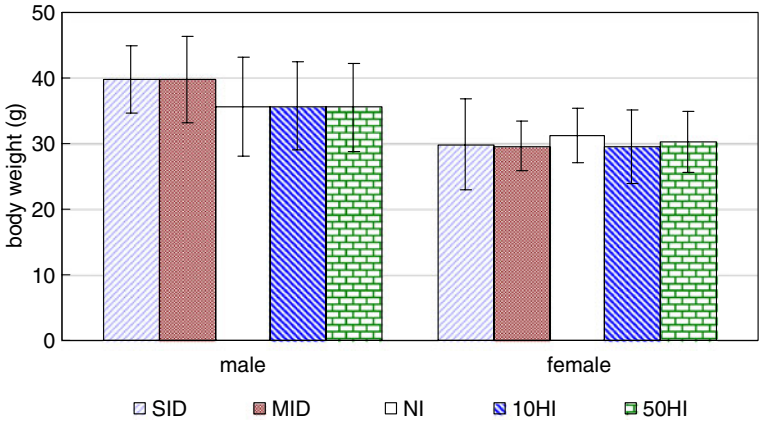

Fig. 1 Body weights of male and female mice with different iodine intakes. Data are shown as mean ± SD. n=13 mice/group

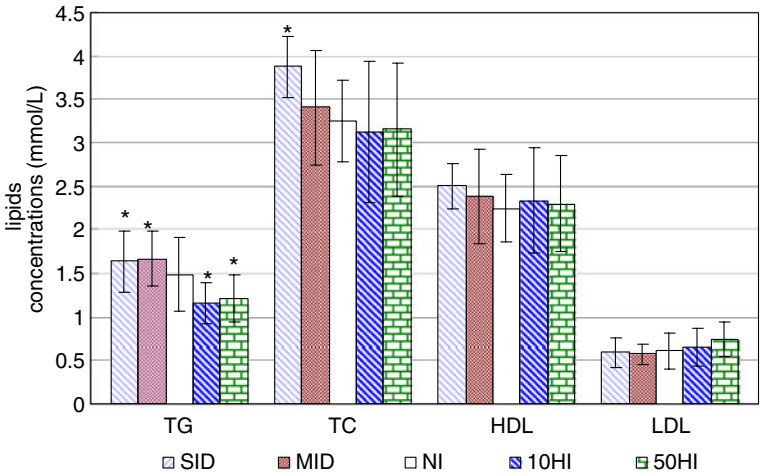

Fig. 2 Lipids concentrations in male mice with different iodine intakes. Data are shown as mean ± SD. n= 13 mice/group. p value indicates difference between groups by analysis of variance. *p<0.05 vs NI group

Determination of Serum Lipids Concentrations in Each Group

The levels of serum TG, TC, and LDL were increased at varying degrees in iodine deficiency groups. In SID group, the levels of TG and TC were much higher than NI group in the male mice (p<0.05) and in the female mice, the levels of TG and LDL were significantly increased (p<0.01). In MID group, only the levels of TG in the male mice and LDL in the female mice were statistically increased (p<0.05 and p<0.01, respectively).

In contrast, a tendency to decrease in the levels of TG and TC could be found in iodine excess groups. The levels of TG in the male mice and TC in the female mice were significantly decreased in both 10 HI and 50 HI compared with NI group, p<0.05 and p< 0.01, respectively (Figs. 2 and 3).

Determination of Serum Thyroid Hormones Concentrations in Each Group

The levels of TT_4, TT_3, FT_4, and FT_3 were all dramatically decreased in iodine deficiency groups especially in SID group compared with NI group (p<0.01 or p<0.05). No

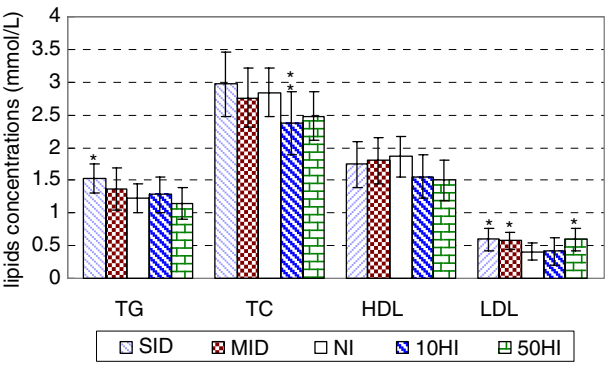

Fig. 3 Lipids concentrations in female mice with different iodine intakes. Data are shown as mean ± SD. n=13 mice/group. p value indicates difference between groups by analysis of variance. *p<0.05; **p<0.01 vs NI group

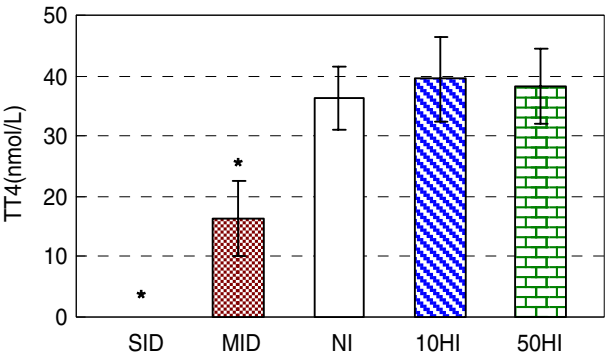

Fig. 4 Serum TT4 concentrations in mice with different iodine intakes. Data are shown as mean ± SD. n=26 mice/group. p value indicates difference between groups by analysis of variance. *p<0.01 vs NI group

significant differences were found between iodine excess groups and normal iodine group (Figs. 4, 5, 6 and 7).

Discussion

Various forms of iodine are absorbed through intestinal tract and then distributed in the extracellular fluid or secreted with saliva, gastrointestinal fluid, and galacta. Thyroid gland is an active iodine-trapping organ, which concentrates iodide from the extracellular fluid and oxidizes it at the aptical membrane, attaching it to tyrosyl residues within thyroglobulin (Tg) and producing thyroid hormones. Redundant iodine (more than 90% of dietary iodine) in body is excreted with urine. Therefore the index of urine iodine concentration is considered as an excellent indicator for assessing the amount of iodine intake. In our study, results showed a parallel between the urine iodine concentration and the amount of iodine intake in each group, which indicated the animal model of deficient-iodine and excess-iodine intake established successfully.

Iodine represents an essential element in thyroid physiology, being a critical component of T_4 and T_3 molecules, and a key regulator of thyroid gland function. Thus dietary iodide supply influences the functional activity of the thyroid gland and iodine deficiency leads to inadequate thyroid hormones production, which can affect the metabolism of serum lipids. Our results showed that in iodine deficiency groups, the levels of TT_4, TT_3, FT_4, and FT_3 were all dramatically decreased compared with NI group especially in SID group. Simultaneously, the levels of serum TG, TC, and LDL were increased statistically at

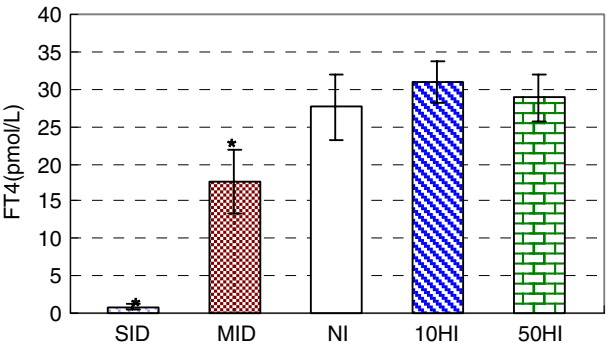

Fig. 5 Serum FT4 concentrations in mice with different iodine intakes. Data are shown as mean ± SD. n=26 mice/group. p value indicates difference between groups by analysis of variance. *p<0.01 vs NI group

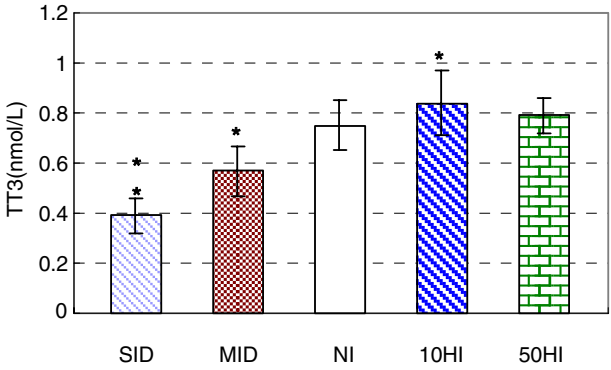

Fig. 6 Serum TT3 concentrations in mice with different iodine intakes. Data are shown as mean ± SD. n=26 mice/group. p value indicates difference between groups by analysis of variance. *p<0.05; **p<0.01 vs NI group

varying degrees. Several mechanisms that have been reported can explain such changes of the serum lipids in iodine deficiency mice. Firstly, the activity of hepatic LDL receptors is under hormonal control. Low level of thyroid hormones may inhibit LDL receptor expression and thus reduce the quantity and activity of LDL receptor leading to an increase of plasma LDL cholesterol [5]. Secondly, low level of thyroid hormones may depress the reactivity of target tissues to catecholamine, growth hormone, cortisol, and glucagons. Thirdly, the amount and the activity of adenyl cyclase and lipoproteinesterase may be reduced owing to the low level of thyroid hormone.

In Turner's experiment, rabbits fed with a cholesterol-rich diet and T4 showed slight to moderate aortic atherosclerosis. Rabbits fed with cholesterol and with either desiccated thyroid or iodine showed an absence of atherosclerotic lesions. Furthermore, average blood cholesterol levels of these animals were significantly lower than the group fed with a cholesterol-rich diet and T4 [6]. It is also reported that treatment of dyslipidemia with T4 had been limited to hypothyroid and subclinical hypothyroid subjects and no curative effects on euthyroid patients with cardiovascular diseases or dyslipidemia [7]. All these researches implied that iodine appeared to have a number of natural physiological roles independent of its role in thyroid hormones. Our results also provided experimental evidence supporting such deduction. In our study, there were no significant differences of the levels of thyroid hormones in the serum between iodine excess groups and normal iodine group. However, a marked decrease in the levels of TG or TC was found in iodine excess groups. Of the body's iodine, only 30% is concentrated in the thyroid tissue and thyroid hormones. The remaining nonhormonal iodine is found in a variety of tissues, and the function is unknown [8]. Accumulating evidences have revealed that iodine has the

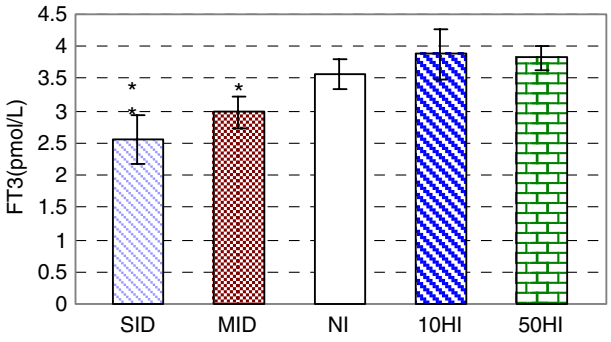

Fig. 7 Serum FT3 concentrations in mice with different iodine intakes. Data are shown as mean ± SD. n=26 mice/group. p value indicates difference between groups by analysis of variance. *p<0.05; **p<0.01 vs NI group

anti-proliferation and anti-oxidation function. It reported that iodide could act as an electron donor in the presence of hydrogen peroxide, peroxidase, and some polyunsaturated fatty acids, thus decreasing damage by free oxygen radicals [9–11]. Concentrations of iodine as low as 15 μg have the same antioxidant activity as ascorbic acid [12]. In addition, animal studies [13] have shown iodine normalizes elevated adrenal corticosteroid hormone secretion related to the stress response and reverses the effect of hypothyroidism on the ovaries, testicles, and thymus in thyroidectomized rats. Iodine may also have a role in immune function; when placed in a medium containing 10^{-6} M iodide, human leukocytes synthesize thyroxine [14]. With regard to the detailed mechanism of the effects of excessive iodine on the serum lipid metabolism, further studies are needed to explore.

In addition, the present study also revealed that excessive iodine's effects on the lipid metabolism may not be the same in different genders in mice. The levels of TG in male mice in iodine excess groups were significantly decreased than that of the same gender of NI group ($p<0.05$). The levels of TC in the female were statistically reduced than that of the same gender of NI group. That the sex hormones have a certain effect on the lipid metabolism has been recognized for many years. Peinado-Onsurbe et al. [15] reported androgen could influence rat HL while estrogen reduced adipose tissue LPL activity and mRNA levels. It has been shown that estrogen may stimulate LDL receptor expression and lower plasma LDL cholesterol [16]. Recently, Kavanagh et al. [17] reported that estrogen could reduce the enzymatic activity of ACAT 2 (acyl-CoA: cholesterol acyltransferase 2) at the protein level, thus reducing hepatic secretion of ACAT2-derived cholesteryl esters in plasma lipoproteins. The mechanism involved in the interaction of excessive iodine and sex hormones on the lipid metabolism needs further studying.

Elevated blood lipids are a risk factor of cardiovascular diseases. Several natural physiological roles of iodine independent of its role in thyroid hormones have been found including anti-microbial, anti-inflammatory, anti-proliferative activities, and reducing blood viscosity which may be also important for overall cardiovascular health [18]. In conclusion, monitoring the iodine intake during sodium restriction is deemed essential for the maintenance of cardiovascular health.

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