Review

The Role of Zinc in Thyroid Hormones Metabolism

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Abstract: Thyroid hormones play an important role in body homeostasis by facilitating metabolism of lipids and glucose, regulating metabolic adaptations, responding to changes in energy intake, and controlling thermogenesis. Proper metabolism and action of these hormones requires the participation of various nutrients. Among them is zinc, whose interaction with thyroid hormones is complex. It is known to regulate both the synthesis and mechanism of action of these hormones. In the present review, we aim to shed light on the regulatory effects of zinc on thyroid hormones. Scientific evidence shows that zinc plays a key role in the metabolism of thyroid hormones, specifically by regulating deiodinases enzymes activity, thyrotropin releasing hormone (TRH) and thyroid stimulating hormone (TSH) synthesis, as well as by modulating the structures of essential transcription factors involved in the synthesis of thyroid hormones. Serum concentrations of zinc also appear to influence the levels of serum T3, T4 and TSH. In addition, studies have shown that Zinc transporters (ZnTs) are present in the hypothalamus, pituitary and thyroid, but their functions remain unknown. Therefore, it is important to further investigate the roles of zinc in regulation of thyroid hormones metabolism, and their importance in the treatment of several diseases associated with thyroid gland dysfunction.

Keywords: Metabolism, thyroid gland, thyroid hormones, zinc

Introduction

The thyroid is an endocrine gland whose follicular cells synthesize and secrete metabolic thyroid hormones triiodothyronine (T3) and thyroxine (T4). These hormones play an important role in the maintenance of body homeostasis. They regulate metabolism of lipids and glucose, facilitate metabolic adaptations in response to changes in energy intake, and control basal metabolism, thermogenesis, as well as oxidative metabolism [1–3]. Thyroid dysfunction can affect all tissues within the body, as many tissues express receptors for thyroid hormones and are dependent on their activity for proper cell function. Thus, normal functioning of the target tissues require adequate intracellular levels of these hormones [4–6]. T4 is the main hormone produced by the thyroid gland. However, T3 is metabolically more active due to its higher affinity for nuclear receptors of thyroid hormones. Intracellular conversion of T4 to T3 is catalyzed by deiodinases enzymes, which act to remove iodine molecules from T4, and this conversion acts like the main regulator of plasma and tissue thyroid hormone concentrations [7–10].

Previous studies have shown the importance of nutrients in regulating the metabolism of thyroid hormones. Zinc in particular, is essential for the synthesis of thyroid hormones as well as its actions on target tissues. Zinc is required for synthesis of the thyrotropin releasing hormone (TRH), plays an important role in the binding of T3 to its nuclear receptor, participates in the synthesis of the thyroid stimulating hormone (TSH) in the anterior pituitary, and acts as an inhibitor or cofactor of type 1 and type 2 deiodinases [11–15]. Therefore, considering the importance of thyroid hormones in the maintenance of the body homeostasis and the action of zinc on the metabolism of these hormones, we aim to clarify the effect of zinc in the mechanisms involved in the regulation of thyroid hormones metabolism.

Physiological and metabolic aspects of zinc

After iron, zinc is the second most abundant transition metal in living organisms, and is also one of the most

important trace elements for energy metabolism. This mineral functions as a cofactor for over 300 metalloenzymes such as carbonic anhydrase, alcohol dehydrogenase and alkaline phosphatase, which participate in carbohydrate, lipid and protein metabolism and in addition to that, zinc is an integral component of zinc finger proteins that regulate DNA transcription [16–19]. Zinc is also important for proper operation of the immune system, antioxidant activity, sensorineural function and structural stability of membranes, transcription/translation of polynucleotides, and endocrine function, especially thyroid hormone metabolism [20, 21]. A healthy adult has 2-3 g of zinc distributed in all tissues, fluids and secretions, with approximately 90% in skeletal muscles and bones, 11% in liver and skin, and the remaining in other tissues. Only a small portion (about 0.5%) of total zinc content in the body is found in the blood. From this total, 80% are present in erythrocytes and approximately 16% in plasma [16, 22]. Inside the cells, about 50% of the zinc in the cytoplasm is 30 to 40% in nucleus and 10% in the plasma membrane [23].

Zinc homeostasis in the body is regulated by adaptive mechanisms that control both mineral absorption and excretion. Zinc can be absorbed via carrier proteins as well as by simple diffusion, which is concentration dependent. Zinc absorption occurs primarily in the proximal small intestine, and is regulated by enterocytes carriers. In addition, absorption efficacy is also dependent on its luminal concentration of the mineral, where higher rates of absorption occurs when the amount of zinc in diet is low [22, 24]. In the intestinal cells, metallothionein is responsible for the homeostatic regulation of zinc absorption. Some factors can influence metallothionein gene expression, including glucocorticoids and high intake of dietary zinc. Another protein present in the intestinal mucosa is the cysteine rich intestinal protein (CRIP), which acts as zinc intracellular carrier, increasing its rate of absorption in deficiency situations. Metallothionein also regulates the binding of zinc CRIP, reducing absorption of this nutrient when there is high intake [25]. Subsequent to the absorption process, zinc is transported into the circulation through the basolateral membrane of enterocytes. It is then transported to the liver by binding to proteins, and from there, distributed to various target tissues. Zinc excretion occurs through kidneys and skin, shedding of epidermal cells, and especially through feces [26].

Zinc cellular homeostasis is maintained by a sophisticated regulation between absorption, distribution, storage and efflux proteins, being zinc transporters and metallothionein, which are fundamental to this process [23]. The SLC39 family, also known as ZIP (Zrt-and Irt-like proteins), increase cytoplasmic zinc concentration by promoting its uptake from extracellular environment or its release from vesicles into the cytoplasm. The SLC30 family of ion transporters, or ZnTs (Zinc transporter), controls zinc efflux from the cytoplasm to the intracellular vesicles or the extracellular space, which contributes to zinc availability in plasma, allowing this mineral to perform its physiological functions [27]. In humans, there are 14 members of the ZIP family and 10 of ZnT family. In zinc excess situations in the body, this micronutrient binds to the metal-responsive transcription factor 1 (MTF-1), which induces the transcription of genes involved in reducing toxicity to high concentrations of zinc such as metallothionein, ZnT1 and ZnT2. When high, MTF-1 also inhibits the expression of genes involved in the uptake of zinc, such as Zip10. However, these mechanisms are not clearly elucidated [28].

The daily zinc intake recommendation is based on the estimated amount of mineral that is needed to restore the contents excreted from the body [24]. The recommended dietary intake (Recommended Dietary Allowance - RDA) for this mineral is 11 mg / day and 8 mg / day for men and women, respectively. During pregnancy and lactation, the RDA for zinc is 11 mg / day and 12 mg / day, respectively. In pregnancy, the average rate of zinc and fetal tissue accumulation increases gradually and since no compensatory change is observed in intestinal excretion of this mineral, it is necessary to increase its daily offering in diet. In relation to lactation, the higher zinc supply aims to compensate the loss of mineral that occurs within the first 4 weeks after birth, since the involution of uterus and reduction of the maternal blood volume can lead to loss of up to 30 mg of zinc accumulated during gestation [29]. Zinc is widely found in animal foods bound to proteins, mainly in meat, poultry, fish, liver and seafood. Whole grains, beans and soy products are also good dietary sources of this mineral [30, 31].

There is no consensus on which indicators are best to use for the determination of zinc status of a population, however this assessment has been performed by evaluation of several biochemical markers [32]. Plasma zinc is currently a biomarker widely used in a population scale, indicated to assess more recent changes in zinc homeostasis, since this biochemical indicator responds to hormonal changes and to the food intake of the mineral [33, 34]. Measurement of erythrocyte zinc concentration, however, do not reflect recent changes of this mineral in the body due the long half-life (120 days) of erythrocytes and has been used as a biochemical parameter in evaluating previous nutritional status for this mineral. However, many factors can change plasma zinc, such as infection, inflammation, hemolysis, stress, and homeostatic control, indicating a false deficiency of the mineral. Nevertheless, the amount of zinc in erythrocytes shown to be unstable in a population of similar subjects in reason of these factors, and may confound the interpretation of results. [35, 36].

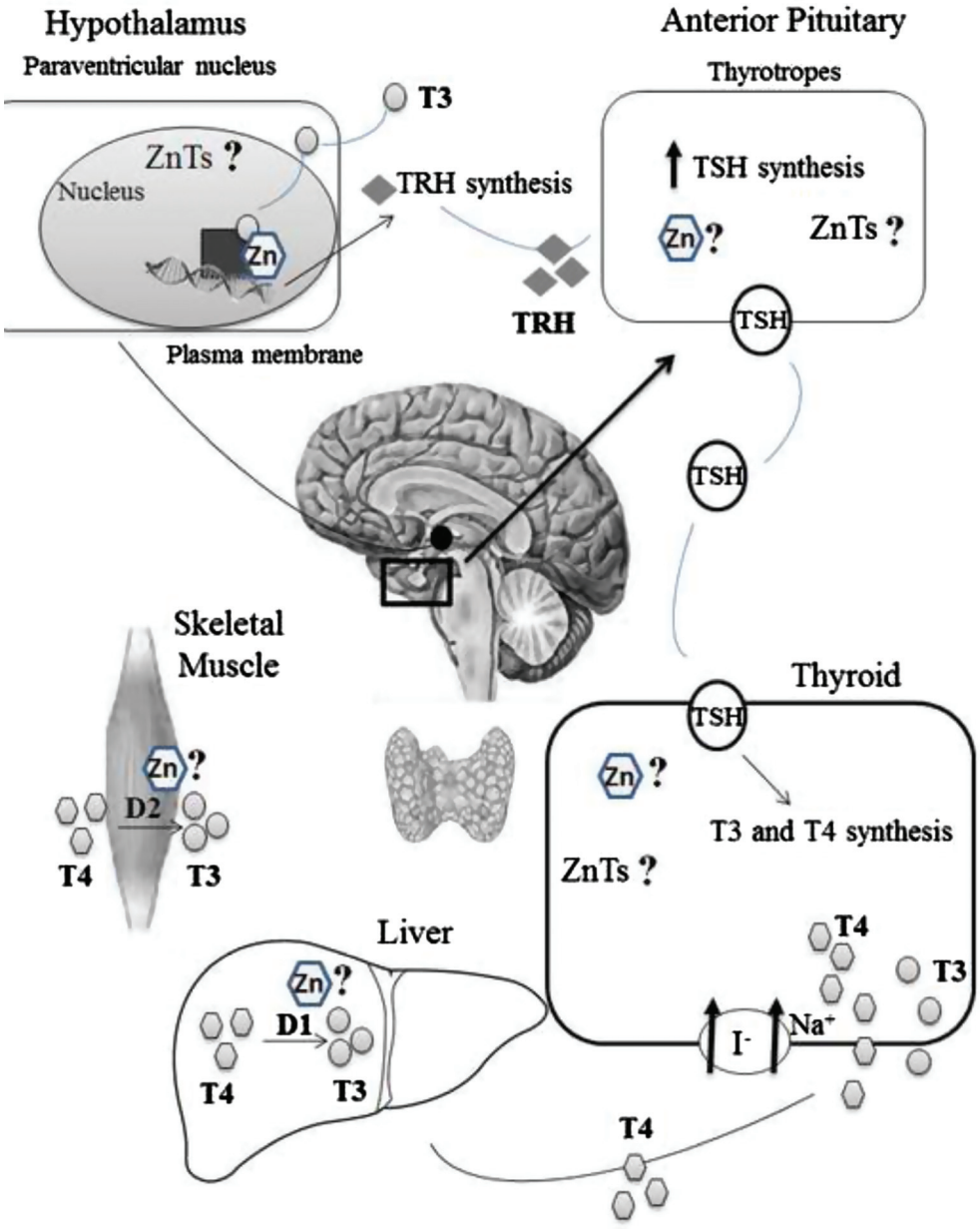

Figure 1. Zinc participation in thyroid hormone metabolism. D1: Type 1 deiodinase; D2: Type 2 deiodinase; I-: Iodide; Na+: Sodium; T3: Triiodothyronine; TRH: Thyrotropin Releasing Hormone; TSH: Thyroid Stimulating Hormone; Zn: Zinc; ZnTs: Zinc Transporters. Zinc acts as a link betweenT3 and its nuclear receptor in the hypothalamus to stimulate the synthesis of TRH. TRH stimulates the synthesis and release of TSH by thyrotrophs in the pituitary glands. TSH stimulates the synthesis of thyroid hormones T4 and T3, which are released into the blood stream. T4 enters tissues such as the liver and the skeletal muscle, where it undergoes deiodination by D1 or D2, respectively. Studies have shown that ZnTs are present in the hypothalamus, pituitary and thyroid, but their functions remain unknown.

Currently there is no accurate, sensitive, and universally accepted method for the assessment of the nutritional status of zinc, which is needed to expand our limited understanding of possible associations between this trace element and chronic diseases. However, the growing technical advances in genome and proteome analyses may be useful for understanding of cellular zinc homeostasis, and also may lead to the discovery of new markers for the evaluation of this mineral.

Zinc and thyroid hormone metabolism

Thyroid hormone is synthesized within the molecule structure of thyroglobulin, where iodine is incorporated into thyroglobulin in a process called organification. Iodide is taken up by thyroid follicular cells through sodium-iodide symporter in a process that is dependent on the electrochemical

Table 1. Studies that evaluate participation of zinc in deiodinases activity.

Ref	Samples	Experimental design	Results
Dhawan et al. [40]	Wistar rats	Supplementation with zinc sulphate in water (227 mg/L) for eight weeks.	Increased D1 activity.
Eybl et al. [41]	Wistar rats	Supplementation with zinc sulfate heptahydrate in water (515 mg/L) for six weeks.	There was no effect on the D1 activity.
Fujimoto et al. [44]	Male wealing rats	Group A: Fed a severe zinc-deficient diet for 5 weeks (1.98 ppm);	Rats fed with a severe zinc-deficient diet had serum T4 and T3 levels significantly diminished;
		Group B: Pair-fed a control group for group A; Group C: Fed a less severe zinc-deficient diet for 5 weeks (6.10 ppm);	Reduced T4 to T3 conversion;
		Group D: Pair-fed control group for group C;	There was a positive correlation between T4 to T3 conversion and alcohol dehydrogenase enzyme activity (marker of zinc hepatic content).
		Group E: Fed a zinc-supplemented control diet for 5 weeks (90.4 ppm of zinc carbonate); Group F: First fed the severe zinc-deficient diet for 5 weeks (1.98 ppm) and then the zinc-supplemented diet (90.4 ppm of zinc carbonate).	
Chen et al. [46]	Male mice	Group A: Lean controls with a basal zinc diet (5 mg/kg diet);	Reduction only in liver D1 activity in obese rats (group D).
		Group B: Lean controls with a zinc-supplemented diet (200 mg/kg diet); Group C: Obese mice with a basal zinc diet (5 mg/kg diet); Group D: Obese mice with a zinc-supplemented diet (200 mg/kg diet).	

D1: Type 1 deiodinase; T3: Triiodothyronine; T4: Thyroxine.

As a regulator of thyroid hormone metabolism, zinc is essential for the synthesis of TRH, since it mediates the binding of T3 to its nuclear receptor and subsequent gene transcription. In addition, it may affect the synthesis of TSH in the anterior pituitary. Furthermore, it also acts as an essential transcription factor for gene expression of proteins involved with thyroid hormone production [11–13, 41, 47]. The thyroglobulin and thyroperoxidase genes have binding sites for transcription factors, and among these, thyroid transcription factor 1 and 2 (TTF-1 and TTF-2) play major roles in gene transcription. TTF-2 is a zinc finger protein that binds to DNA, and is regulated by redox state of cell [48].

Scientific evidence has demonstrated that zinc finger proteins domains in thyroid hormone receptors play a key role in mediating site-specific binding to target response elements and in receptor dimerization. Accordingly, mutations to thyroid hormone receptors which disrupt zinc finger function, impair receptor dimerization or DNA binding capacity [49]. Mutation in ZNF764 (zinc finger protein 764) in a 7-year-old has been shown to induce multiple resistance to hormones, particularly TSH, evidenced by elevated serum concentrations, and lower expression of mRNA for three responsive genes to thyroid hormones (Kruppel-like factor 9, KLF9; glucose-6 phosphate dehydrogenase, G6PD, malic enzyme 1, ME1) compared to normal subjects. However, there was an adequate expression of thyroid hormone receptors. In this sense, the authors suggest that this resistance to thyroid hormones can be explained by the interaction of zinc fingers with coactivators of thyroid hormone receptors, necessary for the start of transcriptional activity [50].

In 1980, Morley *et al.* [51] showed that zinc-deficient rats had lower T3 and T4 levels when compared with those fed the appropriate amount of zinc. Studies carried out by Ertek *et al.* [13], showed a positive correlation between serum zinc concentrations and free T3 in euthyroid individuals and TSH levels in women with normal thyroid function, nodular goiter, and autoimmune thyroiditis. On the other hand, Brandão-Neto *et al.* [41] found that a single oral dose of zinc had no effect on TSH concentrations in healthy men.

Zinc also appears to protect the thyroid dysfunction induced by cadmium by reducing metal concentration, maintaining gland weight and restoring the concentrations of thyroid hormones to normal levels after a diet rich in ethanol [52–54]. Zinc supplementation also increases free T3 serum levels in overweight and obese hypothyroid women [55]. Blazewicz *et al.* [56] analyzed zinc content in the thyroids of patients with nodular goiter and observed that these patients showed a reduction in thyroid zinc content (41.83 ± 7.19 mg/g) compared to the control group (101.30 ± 10.90 mg/g). Patients with goiter also showed reduced serum concentrations of zinc and high excretion of the mineral in the urine [57, 58].

Furthermore, zinc also seems to play a role in maintaining the volume and structure of the thyroid gland, as evidenced in some studies [13, 53, 59]. Ruz *et al.* [51] showed that zinc deficiency caused severe structural changes in follicular cells of thyroid gland in mice, including evidence of cell apoptosis. A possible role of zinc in the thyroid gland is the maintenance of antioxidant balance, since zinc acts as a cofactor for superoxide dismutase and is important for the activity of glutathione peroxidase [13, 59, 60].

gradient generated by the Na+/K+ ATPase (sodium-potassium adenosine triphosphatase). In thyroid follicles, iodide is first oxidized by the enzyme thyroperoxidase in the presence of hydrogen peroxide (H_2O_2) produced by NADPH-dependent oxidase enzyme (nicotinamide adenine dinucleotide phosphate-oxidase). This then allows for the incorporation of iodine atoms onto the tyrosine residues of thyroglobulin present in the colloidal lumen. Thyroperoxidase also catalyzes the coupling reaction between monoiodo-tyrosyl and diiodo- tyrosyl moieties (end-products of thyroglobulin iodination) to form iodothyronines [37].

Table 2. Studies that evaluate the effect of zinc on thyroid hormones concentrations.

Ref	Samples	Experimental design	Results
Baltaci *et al.* [52]	Male adult Sprague–Dawley rats (n = 40)	Group A (controls): Fed a normal rat diet containing 97 mg Zn/kg feed. Group B (Zn): In addition to the standard diet, the animals in this group received intraperitoneal (IP) injections of zinc sulfate at a dose of 3 mg/kg for 4 weeks. Plasma zinc, free- and total triiodothyronine (T3), thyroxine (T4) and thyroid-stimulating hormone (TSH) levels.	Group B showed higher serum concentrations of T3, T4, and TSH when compared to group A ($p < 0.01$).
Mahmoodianfard *et al.* [55]	Overweight and Obese Hypothyroid Women (n = 68)	Group A: Zn + Se (ZS; 30 mg Zn as zinc-gluconate and 200 mg Se as high-selenium yeast, for 12 weeks). Group B: Zn + placebo (30 mg Zn as zinc-gluconate and 200 mg Se as high-selenium yeast, for 12 weeks). Group C: Se + placebo (200 mg Se as high-selenium yeast, for 12 weeks). Group D: placebo + placebo (for 12 weeks). Serum Zn, Se, free and total triiodothyronine (fT3 and fT4), free and total thyroxine (tT4 and tT4), thyroid- stimulating hormone (TSH).	The free T3 serum levels increased significantly in groups A and B, being more significant for group A ($p < 0.05$). Also increased the ratio T3: free T4 in the group supplemented with zinc only ($p < 0.05$).
Ertek *et al.* [13]	Men (n = 62); Women (n = 139)	Group A: Normal Thyroid Subjects (n = 64); Group B: Nodular Goiter Subjects (n = 70); Group C: Patients with Autoimmune Thyroid Disease (n = 64); Serum zinc, serum free T4 and T3, TSH, anti-thyroglobulin and anti-thyroid peroxidase levels.	There was a positive correlation between TSH levels and serum concentrations of zinc in the evaluated women ($p = 0.042$). The authors found a positive correlation between T3 levels and serum zinc (group A; $p < 0.001$). There was a negative correlation between zinc and free T3 (group B; $p = 0.007$). There was a negative correlation between the volume of the thyroid and zinc levels (group B; $p = 0.045$). There was a positive correlation between TSH and serum zinc (group C; $p = 0.049$). Zinc was also correlated with the anti-thyroglobulin Ab levels (group C; $p = 0.002$).
Khandro *et al.* [57]	Goitrous Patients	Group A: Goitrous male (n = 60) (30 mg/dia de zinco, durante 6 meses). Group B: Female patients (n = 72) (30 mg/dia de zinco, durante 6 meses) Group C: Male non-goitrou (n = 106); Group D: Female non-goitrou (n = 120)	The results demonstrated reduced serum concentrations of zinc and high urinary concentrations in patients with goiter (groups A and B) compared with the control group (groups C and D) ($p < 0.007$ and $p < 0.006$, respectively); After supplementation patients showed increased serum concentrations of thyroid hormones (groups A and B); The correlation analysis conducted in study shows positive correlation between serum and urinary concentrations of zinc and T3, T4 and TSH serum (groups A and B, $p < 0.05$)
Morley *et al.* [44]	Male Sprague-Dawley rats	Group A: Rats fed a zinc-deficient diet *ad libitum*; Group B: Rats fed a zinc sufficient, control diet but growth restricted;	Groups A, B and D had lower T3 and T4 levels when compared to the Group C; TSH levels were not significantly different in any of the groups; Hypothalamic TRH content was decreased in Groups A compared to Group C;

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Table 2. (Continued)

Ref	Samples	Experimental design	Results
		Group C: Rats fed a zinc sufficient, "control" diet *ad libitum*; Group D: Rats fed a zinc deficient diet *ad libitum* and hand fed 15 mg of Vitamin A twice a week.	Thyroid weights were increased in Groups A, B and D compared to Group C.

fT3: free Triiodothyronine; fT4: free Thyroxine; Se: Selenium; T3: Triiodothyronine; T4: Thyroxine; TSH: Thyroid Stimulating Hormone; tT3: total Triiodothyronine; tT4: total Thyroxine; Zn: Zinc.

Another important aspect on the topic involves the effect of thyroid dysfunction on the distribution of zinc in the body, which is reflected by changes in their serum concentrations [11, 12]. Pawan *et al.* [61] found a positive correlation between thyroid hormones and Zip10 in the intestines and kidneys, which contributes to zinc transport in rats with induced hyperthyroidism. Furthermore, Prasad *et al.* [62] found that there is retention of zinc in the intestine, liver and renal cortex in animal models with hyperthyroidism. These animals also show lower zinc content and reduced transport of the micronutrient. These results suggest that the distribution of the zinc is affected by the conditions of the thyroid gland. In this sense, serum zinc concentrations appear to be compromised in patients with chronic renal failure, due to reduced intestinal and renal absorption caused by hypothyroidism, which is often found in these patients [63].

Table 3. Studies that evaluate effects of thyroid hormones on zinc metabolism.

Ref	Samples	Experimental design	Results
Pawan et al. [61]	Male albino Wistar rats (n=6)	Group A (Eu-T): Euthyroid rats	Serum T3 and T4 levels were significantly reduced in Group B as compared to Group A whereas these levels were significantly higher in Group C as compared to Group A;
		Group B (Hypo-T): Hypothyroid rats	Zn content in intestine and kidney of Group C was significantly higher than that of Groups A and B;
		Group C (Hyper-T): Hyperthyroid rats	Group C showed a significant increase in the initial (5 min) uptake in both the intestinal and renal BBMV compared to Groups A and B. In contrast, Group B showed a significant decrease in initial uptake of Zn; Expression of 550 bp internal fragment of Slc39a10 gene in both intestine and kidney was found to be significantly increased in Group C and significantly decreased in Group B as compared to Group A.
Prasad et al. [62]	Male young Wistar rats (n=6)	Group A (Eu-T): Euthyroid rats;	Serum T3 levels were reduced significantly in Group B compared with Groups A and C;
		Group B (Hypo-T): Hypothyroid rats;	Zn content in the intestine, liver, and kidney cortex of Group C was significantly higher than the corresponding organs of Groups A and B;
		Group C (Hyper-T): Hyperthyroid rats.	Group C showed a significant increase in the initial uptake in both intestinal and renal BBMV compared with Groups A and B, and Group B showed a significant decrease in initial uptake of zinc; Group C showed a significant increase in the maximal Zn transport activity in the intestinal and renal BBMV and Group B had significantly lower maximal Zn transport activity;
Chen et al. [63]	Male adult Sprague–Dawley rats (n = 36)	Group A (controls): Normal rats	Group B showed a significant decrease in the rate of intestinal zinc absorption and in response of plasma zinc levels as compared with Group C;
		Group B (Hypo-NxT): Rats with two- stage 5/6 Nx to induce CRF and induced hypothyroidism;	Group B also had significantly lower levels of mucosal zinc and MT and a lower content of liver zinc than Group C after intestinal perfusion for 80 min;

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Table 3. (Continued)

Ref	Samples	Experimental design	Results
		Group C (Eu-NxT): Rats with 5/6 Nx and normal thyroid.	Group B showed a lower plasma zinc levels, but had similar output of pancreaticobiliary zinc and the excretion of 24-hour urine zinc than Group C; Group B had a higher excretion of urinary zinc when were used 2% alcohol intestinal perfusion to produce water diuresis.

5/6 Nx: five-sixths nephrectomy; BBMV: Brush-border Membrane Vesicles; CRF: Chronic Renal Failure; D1: Type 1 deiodinase; MT: Metallothionein; T3: Triiodothyronine; T4: Thyroxine.

Research by Zhong *et al.* [64] found expression of the zinc transporters proteins ZnT1-4 and ZnT6, and lower expression of ZnT5 and ZnT8-10 in the thyroid gland of rats, suggesting that these proteins are involved in the regulation of zinc metabolism in this gland as well as the synthesis and homeostasis of thyroid hormones. In addition, expression of the ZnTs 1-10 was also observed in cells of the hypothalamic-pituitary axis, which may indicate the involvement of zinc in the synthesis and release of TRH and TSH. Rogowicz-Frontczak *et al.* [65] showed the presence of autoantibodies ZnT8 as a biomarkers of autoimmune thyroiditis and type 1 diabetes, as this zinc transporter protein also acts in the pancreas to facilitate the synthesis and crystallization of insulin. Murgia *et al.* [66] found ZnT8 expression in the cuboidal epithelial cells of the thyroid gland in mice, and these cells were enriched in labile zinc, suggesting a role of this protein in the compartmentalization of zinc for the vesicles, which is required for secretion of specific hormones. Lastly, Ruz-Riol *et al.* [67] demonstrated high expression of metallothionein protein in the thyroid gland tissues, with cytoplasmic and irregular distribution in patients with Graves' disease. It was suggested that inflammatory cytokines infiltrating the thyroid gland in patients with Graves' disease can induce the expression of metallothionein as an immunoregulator to act as a defense mechanism against inflammation, and restore homeostasis.

Proteases digest iodinated thyroglobulin, which leads to the release of biologically active thyroid hormones into the blood stream. In tissues, these hormones, in particular T3, bind to specific nuclear receptors, and regulate the transcription of target genes. Mono and diiodo-thyronines are also produced during proteolysis. However, they do not have hormonal action, and are deiodinated in order to recycle iodine in the thyroid gland [8].

T4 is the main hormone produced by the thyroid gland, and accounts for about 93% of the total amount of secreted hormones. Nevertheless, T3 is the most metabolically active hormone with a 10-15 fold increase in affinity for thyroid hormone receptors as compared with T4. Therefore, intracellular conversion of T4 to T3 by deiodinases enzymes in necessary to ensure high functional efficiency of thyroid hormones [9, 10, 38].

Deiodinases are a group of three selenoproteins consisting of deiodinases 1, 2 and 3 (D1, D2 and D3, respectively), which act by removing iodine from thyroid hormones [7]. D1 is expressed in the liver, kidney and thyroid. It activates thyroid hormones by converting T4 by outer ring deiodination to bioactive T3. In addition, it also degrades thyroid hormones by inner ring deiodination. The action of D1 on the liver and kidneys is the major source of plasma T3. D2, expressed in central nervous system, heart, skeletal muscle, retina, cochlea and brown adipose tissue, is the primary activator of cellular T4, and produces T3 by removing one iodine residue from the phenolic tyrosine ring. D3, in turn, is the main inactivating enzyme of thyroid hormones through conversion of T3 and T4 to the inactive iodothyronines (reverse T3 [rT3] and 3,3'-diiodo-thyronine [T2]), and is expressed in the central nervous system, skin, uterus, placenta and regenerating tissues [10, 39].

Studies conducted with the aim of elucidating the role of zinc on the activity of deiodinases enzymes have demonstrated its ability to function as a cofactor [12, 15]. Dhawan *et al.* [40] found that zinc supplementation in rats increased the activity of thyroid type I disorders related to thyroid gland dysfunction, and in regulation of thyroid hormones levels. However, another study did not show efficacy of zinc supplementation on the activity of this deiodinase in liver rats [41]. In humans, zinc also seems to be a cofactor of type II deiodinase, which is the most active enzyme for T4 to T3 conversion [42, 43].

Fujimoto et al. [44] demonstrated that rats fed with a severe zinc-deficient diet (1.98 ppm) had serum T4 and T3 levels significantly diminished and reduced T4 to T3 conversion. Furthermore, there was a positive correlation between T4 to T3 conversion and alcohol dehydrogenase enzyme activity, a marker of zinc hepatic content, in rats of control group and in those fed with a severe zinc-deficient diet. On the other hand, zinc may also act as an inhibitor of hepatic type I deiodinase [45, 46]. In a study by Chen *et al.* [46], it was found that zinc in high concentrations reduced type I deiodinase activity in animal models, which was also observed *in vitro* (Figure 1 and Tables 1, 2, 3).

Conclusions

Scientific evidence shows that zinc plays a key role in several metabolic reactions, particularly in thyroid hormone metabolism. However, the complex metabolism of this mineral as well as its interactions with thyroid hormones is not fully understood. Therefore, future studies should

aim to clarify the mechanisms involved in the regulation of thyroid hormones metabolism by zinc, and its importance in the treatment of diseases associated with thyroid gland dysfunction.

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Conflict of interest
The authors declare no conflicts of interest.

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