



The Significance and Importance of Trace Elements in the Functioning of Thyroid Gland

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ABSTRACT

Trace elements are essential for health, growth and functioning of a number of components of the immune system. They are very important for a number of enzymes and proteins which are involved in many physiological and biochemical processes related to growth, production and reproduction. There are many trace elements which are associated with thyroid function, among which Iodine is very important as it is the source for thyroid hormones synthesis. Selenium-containing enzymes protect the thyroid gland from oxidative stress and the selenium-based proteins help to regulate hormone synthesis, converting T4 into the more accessible and active T3. These proteins and enzymes help to regulate metabolism and maintain the right amount of thyroid hormones in the organs where it is being used. Similarly trace elements like zinc, iron and copper are vital for thyroid function. In this review, we have summarized all information available on the role of trace elements for the functioning of Thyroid gland. Some trace elements showed increased concentration in malignant and benign thyroid nodules and therefore, those trace elements can also be used as markers of thyroid cancers.

Keywords: Iodine, Selenium, Zinc, Iron, Copper, Thyroid hormones.

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INTRODUCTION

Even though required in very small quantities, trace elements such as iron, iodine, fluoride, copper, zinc, chromium, selenium, manganese and molybdenum are vital for maintaining health. Trace elements are also known as micro minerals which are part of enzymes, hormones and cells in the body. Insufficient intake of trace minerals can cause symptoms of nutritional deficiency. Trace elements play vital roles in immune system and optimal function of a variety of physiological processes¹. Deficiencies or alterations in the levels of these trace elements adversely affect the ability to withstand oxidative stress-mediated cell damage. Schizophrenia is an oxidative stress induced mental illness as indicated by low levels of antioxidant defence enzymes (glutathione peroxidase, superoxide dismutase and catalase)² and antioxidant activity³. Selenium is an important constituent of glutathione peroxidase enzyme. Manganese, copper and zinc are important components of superoxide dismutase (SOD) while iron is found in catalase⁴. Chromium affects level of neurotransmitters through its action on insulin⁵. Cadmium is an extremely toxic metal which displaces zinc in many metallo-enzymes thus causing cadmium-induced zinc deficiency⁶. Lead affects the release of neurotransmitters such as dopamine. Lead causes accumulation of neurotoxic intermediary metabolites⁷ while copper stimulates production of dopamine that enhances brain activity⁸. There are various research works on the role of trace elements on thyroid function and this review paper is an attempt to collect the updated information on the association of trace elements on thyroid function.

Role of Trace Elements on Thyroid Metabolism

Apart from the essential trace element iodine, which is the central constituent of thyroid hormones, a second essential trace element, selenium is required for appropriate thyroid hormone synthesis, activation and metabolism. The human thyroid gland has the highest selenium content per gram of tissue among all organs. Several selenocysteine-containing proteins enzymes are functionally expressed in the thyroid, mainly in thyrocytes themselves: three forms of glutathione peroxidases (cGPx, pGPx, and PH-GPx), the type I 5-deiodinase, thioredoxinreductase and selenoprotein P. The thyroidal expression of type II 5-deiodinase still is controversial. As thyrocytes produce H₂O₂ continuously throughout life an effective cell defence system against H₂O₂ and reactive oxygen intermediates derived thereof is essential for maintenance of normal thyroid function and protection of the gland. Long-term selenium deficiency leads to necrosis and fibrosis after high iodide loads. Inadequate supply of selenium and pre diagnostically low serum levels are significantly correlated with the development of

thyroid carcinoma and other tumors. Though selenium supply controls expression and translation of selenocysteine-containing proteins, no direct correlation is found between selenium tissue content and expression of various thyroidal selenoproteins, indicating that other regulatory factors contribute to or override selenium-dependent expression control such as in thyroid adenoma, carcinoma or autoimmune disease, since both trace elements, iodine and selenium needs to be provided either by a balanced diet or supplementation⁹. The mean concentration of plasma zinc in hypothyroid and in euthyroid patients was lower than that of control subjects, whereas no statistically significant differences were observed in plasma zinc values between hyperthyroid patients and control subjects. The average erythrocyte zinc level in patients with thyroid disease was significantly lower than that in control subjects. Erythrocyte zinc concentration was significantly decreased in hyperthyroidism compared with hypothyroidism, or patients previously either hyperthyroid or hypothyroid but now euthyroid. Increased urinary zinc excretion in hyperthyroidism was noticed compared to euthyroid and hypothyroid patients compared to control subjects. Increased urinary zinc concentrations may result from increased tissue catabolism. The abnormal zinc metabolism occurs commonly in patients with thyroid disease¹⁰. Erythrocyte zinc values were significantly lower than normal in hyperthyroidism and higher in hypothyroidism. A significantly higher than normal urinary excretion of zinc was observed in hyperthyroidism. The mean concentrations of plasma and erythrocyte copper were significantly above normal in hyperthyroidism. Plasma selenium levels were significantly lower than normal in hyperthyroidism. No statistically significant difference was found in plasma zinc, erythrocyte manganese, or urine copper values between patients with thyroid diseases and healthy controls. The erythrocyte manganese content correlated well with thyroxine and triiodothyronine levels. Plasma prealbumin and retinol-binding protein correlated well with the erythrocyte zinc content but not with plasma zinc levels. There was no correlation between erythrocyte superoxide dismutase activity and erythrocyte copper or zinc concentrations. The metabolism of zinc, copper, manganese and selenium is abnormal in thyroid diseases¹¹. Oral administration of mercuric chloride for consecutive days increases thyroid function as noted by an increase in thyroid ¹³¹I release rate. The findings indicate that the influence of mercuric chloride ingestion on thyroid function probably reflects the quantity of mercuric chloride administered and the length of time during which exposure to mercury persists¹². The functional impairment of the pituitary, thyroid, testes and adrenal glands of humans occupationally exposed to mercury vapour can be shown as a result of accumulation of Hg in these glands. Among basal concentrations of thyrotropin (TSH), prolactin, free thyroxine (free T4), free 3,5,3'-

triiodothyronine (free T₃), antibodies against thyroperoxidase and testosterone in serum, as well as cortisol in morning urine, serum free T₄ concentration and the ratio free T₄/free T₃ were slightly, but significantly, higher in the subgroups with the highest exposure and the serum free T₃ was inversely associated with cumulative mercury exposure. This indicates a possible inhibitory effect of mercury on 5'-deiodinases, which are responsible for the conversion of T₄ to the active hormone T₃. Serum total testosterone, but not free testosterone was positively correlated with cumulative Hg exposure. Prolactin, TSH and urinary cortisol concentrations were not significantly associated to exposure. Apart from inhibition of the deiodination of T₄ to T₃, the endocrine functions studied seem not to be affected by exposure to Hg vapour at the exposure levels of an earlier study¹³. Instrumental neutron activation analysis has been used to estimate silver, cobalt, Chromium, Iron, mercury, iodine, rubidium, antimony, scandium, selenium and zinc concentrations in malignant and benign thyroid nodules as well as in apparently intact Para nodular thyroid tissue. In para nodular tissue the silver, cobalt, mercury, iodine and rubidium contents were much higher for malignant and benign nodules than the controls. There was also a slight deficiency of selenium in the nodules compared with the standard, suggesting that the direct toxic heavy metal influence on thyrocytes plays a major role in thyroid cancer aetiology, provided that an adequate level of the defence mechanisms is absent. Iodine concentrations are 15 times lower on an average in malignant compared with benign nodules. It is also shown that the ratio between the iodine concentration in nodular and Para nodular tissue can be used for *in vivo* thyroid cancer diagnostics¹⁴. Iodothyronine 5' deiodinase, which is mainly responsible for peripheral T₃ production, has recently been demonstrated to be a selenium containing enzyme. The structure of nuclear thyroid hormone receptors contains zinc ions, crucial for the functional properties of the protein. In the elderly, reduced peripheral conversion of T₄ to T₃ with a lower T₃/T₄ ratio and overt hypothyroidism are frequently observed. In a study serum selenium and Red Blood Cell Glutathione Peroxidase (RBC GSH-Px) as indices of selenium status, circulating and RBC zinc (as indices of zinc status), thyroid hormones and TSH were measured in euthyroid subjects, carefully selected to avoid abnormally low thyroid hormone levels induced by acute or chronic diseases or calorie restriction. A highly significant linear correlation between the T₃/T₄ ratio and indices of selenium status was observed in the older group of subjects. Indices of zinc status did not correlate with thyroid hormones, but RBC zinc was decreased in older as compared with younger subjects, suggesting reduced peripheral T₄ conversion is related to impaired selenium status in the elderly¹⁵. To know the influence of thyroid hormones on homeostasis of trace elements, a study was conducted on the variation of iron, copper and zinc in erythrocyte

and serum from patients with hyperthyroidism before and after ^{131}I therapy by the X-ray fluorescence method. The different thyroid status of the patients before and after the therapy were assayed by determining the levels of thyroid hormones. The results showed that the homeostasis of metal ions in both serum and erythrocyte could be more or less influenced by the altered thyroid hormones. The serum copper and zinc exhibited the significantly positive correlation with T_3 and T_4 . Although the serum copper and zinc differed significantly before and after the therapy, no difference was observed in the concentrations of copper and zinc in erythrocyte, except that the erythrocyte zinc in the patients with hypothyroidism exhibited an obvious increase. Furthermore, the erythrocyte zinc showed a markedly negative correlation with T_3 ¹⁶. A study investigated the possible differences among the concentrations of copper, zinc and selenium and their mutual relations in the whole blood and thyroid tissue of patients with various thyroid disorders. The mean levels of these elements in blood as well as the mean copper/zinc, copper/selenium and zinc/selenium ratios in the patients with thyroid cancer were significantly higher than in other patients and the control groups. However, the mean zinc and selenium concentrations in the thyroid cancer tissue were significantly lower than in the thyroid tissue of other patients. In addition, the mean copper/zinc and copper /selenium ratios in the thyroid cancer tissue were significantly higher than in the patients with other thyroid diseases, confirming that the highest levels of copper and zinc as well as the copper/zinc, copper/selenium and zinc/selenium ratios in the whole blood of the patients with thyroid cancer may suggest the progression of the proliferation process in the thyroid gland. The low concentrations of zinc and selenium in the thyroid tissue confirm their participation in the carcinogenic process¹⁷. Experimental hyperthyroidism was established and used to investigate possible alterations in the calcium, magnesium and zinc homeostasis by assessing their concentrations in plasma and erythrocytes. L-thyroxine-induced hyperthyroidism condition shows a significant decrease in erythrocyte calcium, magnesium and zinc concentrations and a significant decrease in plasma magnesium concentration. Significant positive correlations were found for magnesium and zinc both in plasma and in erythrocytes. The results suggest that the homeostasis of calcium, magnesium and zinc is altered during experimental hyperthyroidism¹⁸. Normal thyroid status is dependent on the presence of many trace elements both for synthesis and metabolism of thyroid hormones. Selenium is essential for normal thyroid hormone metabolism being involved with selenium-containing iodothyronine de-iodinases that control the synthesis and degradation of the biologically active thyroid hormone, T_3 . Additionally, selenoperoxidases and thioredoxin reductase protect the thyroid gland from peroxides produced during the synthesis of hormones.

The roles of iron, zinc and copper in the thyroid are less well defined but sub- or supra-optimal dietary intakes of all these elements can adversely affect thyroid hormone metabolism¹⁹. Treatment with methimazole increased the magnesium concentration both in erythrocytes and in serum but both urinary output and fractional excretion of magnesium decreased significantly. The erythrocyte sodium concentration decreased with treatment but the serum sodium remained unchanged. Urinary excretion of sodium also decreased with treatment, but only changes in indices of magnesium metabolism (decrease in renal fractional excretion, rise in serum level) correlated significantly with those of the thyroid functions with treatment. These observations clearly indicate that in Graves' disease, the magnitude of magnesium metabolism alteration is closely related to the extent of the increase in thyroid hormones in plasma²⁰. Within the wide spectrum of patients with thyroid disease studied, the most salient feature is that of diminished levels of selenium in cases of sub-acute and silent thyroiditis, as well as in the setting of paediatric patients with hyperthyroidism and poly endocrinopathy, and in cases of differentiated thyroid carcinoma. The mechanisms that lead to low selenium levels are not yet known. Loss of differentiation of thyroid carcinoma has been recently postulated to be related to selenium metabolism²¹. After excluding hyperparathyroidism and malignancy-related hypercalcemia, hypercalcemia was considered to be attributable to the exacerbation of hyperthyroidism with increased bone resorption. The increased dose of thiamazole normalized serum calcium level and thyroid function three months later. Laboratory tests suggest that normal bone formation in spite of increased bone resorption contributed to hypercalcemia in hyperthyroid patients²². The mean values of iodine, iron and selenium in serum and urine samples of thyroid mothers and their infants were significantly lower as compared to the referent mothers-infants pairs. The deficiencies of essential trace elements may adversely affect the health of women and their neonates²³. Intracellular calcium ion concentration may also be subject to regulation by other non-genomic effects of iodothyronines, such as those on the Na^+/H^+ antiporter or sodium current, that secondarily affect the $\text{Na}^+/\text{Ca}^{2+}$ exchanger. Certain of these non-genomic actions of thyroid hormone, such as Na^+/H^+ exchanger, Ca^{2+} -ATPase, are now recognized to begin at a recently described hormone receptor on a heterodimeric structural membrane protein. The thyroid hormone signal at this receptor is further transduced by the mitogen-activated protein kinase pathway²⁴. With respect to the relationship between goitre and inorganic matter of water such as fluoride, magnesium, nitrate and hardness of water, there is no discernable statistically significant difference have been observed between the two groups in relation to inorganic content of water. There was no clear relationship between the inorganic contents of water and

prevalence of goitre²⁵. Until recently, trace minerals were added to diets to control nutritional deficiencies such as anaemia for iron, rough hair coat for zinc and goitre for iodine. However, numerous research in the last two decades have demonstrated the positive effects of additional quantities of trace minerals on other aspects of animal metabolism independent of classical signs of deficiencies²⁶. No evidence of any effect of selenium supplementation on thyroid function, despite significant increases in plasma selenium. However, baseline plasma selenium in a study was somewhat higher than in previous supplementation studies in which apparently beneficial effects were seen²⁷. Recent studies have demonstrated that a high prevalence of iron deficiency among children in areas of endemic goitre may reduce the effectiveness of iodized salt programs. These findings argue strongly for improving iron status in areas of overlapping deficiency, not only to combat anemia but also to increase the efficacy of iodine prophylaxis. The dual fortification of salt with Iodine and Iron may prove to be an effective and sustainable method to accomplish these important goals²⁸. Selenium is found as selenocysteine in the catalytic centre of enzymes protecting the thyroid from free radicals damage. In this way, selenium deficiency can exacerbate the effects of iodine deficiency and the same is true for vitamin A or iron deficiency. Substances introduced with food, such as thiocyanate and isoflavones or certain herbal preparations, can interfere with micronutrients and influence thyroid function²⁹. An important relation between thyroid hormones and zinc has been observed recently and low zinc levels in hypothyroidism and high levels in hyperthyroidism is a significant proof of this relation. Hypothyroidism leads to changes in serum levels of some elements. These changes may be associated with reduced zinc levels in hypothyroidism³⁰. Nongenomic effects of thyroid hormone on calcium pump (Ca^{2+} -ATPase) activity have been documented experimentally and clinical hyper- and hypothyroidism are associated with increased and decreased activities, respectively, of human erythrocyte Ca^{2+} -ATPase activity and ion transport. T_3 stimulation of cardiac sarcoplasmic reticulum calcium pump content and activity have also been shown to be achieved via a genomic mechanism³¹. The objective of an earlier study was to examine changes in trace elements due to thyroid cancer in humans. Serum levels and tissue contents of trace elements were measured in 43 patients with thyroid cancer before and 4 days after surgery were compared to normal values. The serum levels of zinc in cancer patients were lower than those of normal subjects. Surgical removal of the cancer resulted in the restoration of these levels. Although serum copper levels in patients were not different from normal, but post-operatively these levels rose significantly. Levels of iron, magnesium and manganese were significantly lower post-operatively. There was no significant change in serum selenium levels. The thyroid tissue

contents of these trace elements did not show a difference between the normal thyroid tissue and the cancerous lesion. Out of the six trace elements examined, the decrease of serum levels of zinc in cancer patients may be linked to the disease condition. It is suggested that this change may be used to demonstrate successful cancer surgery and may have implications for a long-term follow-up of thyroid cancer patients³². The trace elements studied (selenium, copper and zinc) are the essential constituents or cofactors required to activate numerous enzymes and proteins, playing crucial role in various physiological processes. The disturbed levels of the above mentioned elements may adversely affect the endocrine system, resulting in various thyroid disorders among other upsets. In the group of patients with papillary carcinoma, a statistically significant higher copper concentration was observed in Hashimoto disease. In the same group zinc/copper ratio demonstrated reciprocally arranged statistically significant differences but in a group of papillary cancer patients, there was a negative correlation between lag time since thyroid operation and GPX3 activity. The data support the hypothesis of indirect involvement of zinc and copper in thyroid regulation. For selenium, lack of simple correlation between its serum level and thyroid indices implies the need for further research on the selenium related parameters more adequately depicting changes in endocrine system³³.

CONCLUSION

The contents of this review article have brought into a nutshell the involvement of various trace elements in the synthesis and regulation of hormones of thyroid in both health and disease status. The prominent role played by Iodine, Selenium, Zinc, Copper and Calcium have been highlighted. The non-essential trace element mercury too is also significantly involved in control of thyroid function. Further supplementation studies are required to assess the exact deficiency of trace elements which are involved in controlling the function of Thyroid gland and its hormones. The contents focused in this review article will be useful for researchers to undertake further studies in this important field and to define a set of laboratory diagnostic tool for the evolution of thyroid disorders.

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