Review Article

Trace element status and human endocrine health: A perspective

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Abstract

The presence of trace elements is vital for the smooth functioning of the human body. Although trace elements such as Cr, Cu, Fe, I, Mn, Ni, Se, Zn are present in low concentrations, they are considered as the building blocks of life, participating actively in regulating many biochemical processes. The endocrine system influences every cell in the human body to maintain equilibrium at the cellular level. Imbalance in the homeostasis of hormone production, secretion, manifests in the development of endocrine abnormalities. The specific objective of this article is to perform a comprehensive, detailed evaluation of the adequacy of current research undergoing risk assessment of endocrine-related disorders and its association with trace elements. In this review, we have studied >100 research and review publications on the aforementioned topic. After a thorough investigation it has come to our notice, that although not many, there are a few studies undertaking the investigation of the individual influence of a particular trace element on a focused pathological hormonal disorder. However, there are only a handful of studies investigating the effect of the multiple trace elements and their combined effect on the molecular as well as cellular functions of the human endocrine system.

Keywords: Endocrinology, hormones, minerals, trace elements

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HORMONES

Hormones are natural substances that act like chemical messengers between different parts of the body. They control many functions including growth, reproduction, sexual function, sleep, hunger, mood, and metabolism. Dysregulation in hormonal production or secretion leads to various pathological disorders [Table 1]. The hierarchy of hormone begins in the cortical regions of the brain, where sometimes even conscious neural signals stimulate a hormonal response.[1]

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The overall functioning of the endocrine system depends on many synchronizing factors. Firstly, the endocrine glands must release the proper amount of hormones. The body must have a strong blood supply to transport the hormones around the body. There must be enough receptors to which the hormones can attach and carry out their function. The targets must be capable of responding to the hormonal signal.[1] Thereby, every hormone will then manifest its effects, abnormalities, and symptoms [Table 1].

TRACE ELEMENTS

Trace elements are inorganic constituents present in concentrations <50 mg/kg body weight Table 2.

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Table 1: Physiological functions affected by imbalance in homeostasis of trace elements

Element	RDA for adults*	Effects of deficiency	Effects of excess
Chromium	25-35	Hampers potency of insulin in regulating sugar balance, weight loss, impaired coordination	Worsens insulin sensitivity
Copper	900	Anemia, hair problems, dry skin, Vitamin C deficiency, osteoporosis	Liver damage, nerve damage, cramps, nausea, diarrhea
Iodine	150	Growth retardation, cognitive disability, goiter, miscarriage	Iodine induced hyperthyroidism, fever, abdominal pain, nausea; vomiting diarrhea, weak pulse
Iron	8-18	Anemia, insomnia, palpitations, headaches, difficulty concentrating, brittle nails, cracked lips	Constipation, nausea, liver disease, diabetes mellitus, hypothyroidism
Manganese	1.8-2.3	Osteoporosis, dermatitis, problems metabolizing carbohydrates, poor memory, nervous irritability, fatigue, glucose intolerance, heavy menstrual periods	Tremors, muscle spasms, tinnitus, hearing loss, insomnia, depression, delusions, anorexia, headaches, irritability
Selenium	500	Hypothyroidism, fatigue, goiter, cretinism, mental retardation, and miscarriages	Reversible balding, brittle nails, garlic odor to the breath, intestinal distress, weakness, slowed mental functioning, acute respiratory distress syndrome, myocardial infarction, muscle tenderness, tremors, lightheadedness, facial flushing
Zinc	8-11	Slow healing of wounds, loss of taste, retarded growth, delayed sexual development in children, impaired immune function	Nausea, vomiting, loss of appetite, stomach cramps, diarrhea, headaches, low copper levels, lower immunity, low levels of HDL cholesterol

*RDA: Recommended daily intakes. Concentrations are in mg except for chromium, copper, iodine selenium, which is in μg. HDL: High-density lipoprotein, RDA: Recommended dietary allowances

Table 2: Natural and artificial sources of trace elements

Elements	Natural sources and fortified foods	Supplemental sources
Chromium	Broccoli, potatoes, and green bean, whole-grain products, beef and poultry, apples, bananas, milk, dairy products	Chromium chloride, chromium nicotinate, chromium picolinate, high-chromium yeast, chromium citrate
Copper	Seafood, egg, meat, spices, herbs, sun-dried tomatoes, mushrooms, nuts, chocolates, edible seeds, goat cheese	Cupric oxide, cupric sulfate, copper amino acid chelates, copper gluconate
Iodine	Iodized salt, seaweed, milk, ice cream, cheese, yogurt, butter, fish, sushi, shellfish	Potassium iodide, sodium iodide, kelp containing supplements
Iron	Beans, lentils, tofu, cashews, dark green leafy vegetables, whole-grain, fortified breakfast cereals, breads	Ferrous sulfate, ferrous gluconate, ferric citrate, and ferric sulfate, heme iron polypeptides, carbonyl iron, iron amino-acid chelates, and polysaccharide-iron complexes
Manganese	Oysters, clams, nuts, soybeans and legumes, oatmeal, bran cereals, whole wheat bread, brown rice, leafy green vegetables, pineapple, dark chocolate	Amino acid chelates, manganese aspartate, manganese gluconate, manganese picolinate, manganese sulfate, manganese citrate, and manganese chloride
Selenium	Brazil nut, fish, ham, pork, beef, turkey, chicken, dairy	Selenomethionine, sodium selenite, or sodium selenite
Zinc	Meat, shellfish, oysters, legumes, seeds, nuts, dairy, eggs, whole grains, fortified breakfast cereals	Zinc gluconate, zinc sulfate, and zinc acetate in the form of tablets, capsules, cold lozenges

The average human body consists of 0.02% or 8.6 g of trace elements. This small fraction of the elements, however, plays a crucial role in a myriad of physiological activities. Some of the trace elements control vital biological processes by enhancing the binding of molecules to their receptor sites on the cell membrane, by adapting the structures or ionic nature of membrane to avert or permit certain molecules to invade or exit a cell and in influencing gene expression arises in the generation of protein required in life processes.[2] Homeostasis of trace elements influences biochemical pathways and causes characteristic diseases. Trace metal metabolism may be concerned with intake, dietary availability, absorption, distribution, storage, mobilization, biochemical activity, and excretion. According to Bertrand's law, for each biological system, there is a range of exposure, compatible with and essential for optimal function, and that below and above the range function deteriorates, resulting in disease and ultimately, death. Thus, essential trace elements, like all essential nutrients, present two risks: One of deficiency and another of toxicity. Any intervention to reduce the risk of marginal deficiency must be designed so as not to increase the risk of marginal toxicity by creating imbalances among trace elements.

This review updates on the physiological importance of trace elements in the overall functioning of the endocrine system and its role in maintaining homeostasis of these elements for the proper functioning of the human body.

Chromium

Chromium is an essential component for the biosynthesis of Glucose Tolerance Factor (GFT). Chromium deficiency causes impairment of glucose tolerance while toxicity results in renal failure, dermatitis, and pulmonary cancer.[3] Chromium produces marked increase in enzyme activity and enhances sugar metabolism through insulin activation. It has been demonstrated to be essential in the action of insulin as shown by chromium deficiency studies. Chromium regulates blood insulin levels by activating glucose uptake by the muscles and other tissues. In chromium deficiency, insulin resistance is triggered when the total GFT levels drop down, leading to higher blood sugar levels, stimulating the release of further insulin, which however is ineffective to exert its role.[4] Surplus chromium supplementation in patients with type 2 diabetes may have a satisfactory effect on glycemia and dyslipidemia, whereas these effects are not seen in the patients without diabetes. Jeejeebhoy *et al.* have demonstrated the reversal of glucose

intolerance and neuropathy after supplementation of chromium as a long-term parenteral nutrition dose.[5] Studies done on cultured rat skeletal muscle cells have examined the effect of chromium picolinate on insulin internalization. The increased internalization rate was accompanied by a marked increase in the uptake of both glucose and leucine. The effect was specific for chromium picolinate since neither zinc picolinate nor any of the other forms of chromium tested were effective. The authors postulate increase in membrane fluidity of synaptic liposomal membranes as the reason behind increased insulin internalization.[6]

Copper

Copper has a selected biochemical function in hemoglobin synthesis, connective tissue metabolism, and bone development. Synthesis of tryptophan is done in the presence of Cu. In recent years, imbalance in the homeostasis of both Cu and Zn were linked to chronic disease etiology due to antioxidant properties. Moreover, zinc affects immunological properties and acts together with copper as cofactor of Cu, Zn-superoxide dismutase (SOD). This enzyme protects cells and their important components against free radical damage.

Copper is crucial for the functioning of many enzymes including cytochrome c oxidase, lysyl oxidase and superoxide dismutase forming an integral part of the enzyme's active sites. Copper deficiency during pregnancy results in the death of the embryo. During pregnancy, Cu is transported from the mother to the fetus through two copper transporting ATPase's, namely MNK and WND. A recent study has shown that the regulation MNK and WND is under the influence of insulin and estrogen in the human placental cells. Insulin increases the levels of MNK and thus upregulates the transport of Cu from mother to fetus while the same hormones are involved in removing excess of Cu from the fetus by reducing the levels of WND.[7]

Copper also has been demonstrated to play an active role in human reproduction. Male rats fed with Cu deficient diets exhibited lower levels of Cu in testis, which were linked to lower levels of testosterone. As opposed to male rats, the female rats are better protected against Cu deficiency as a result of endogenous estrogen. Oestrogen alters hepatic subcellular levels of Cu and induces the synthesis of ceruloplasmin.

Zhang *et al.* have investigated the effect of thiodiazole copper on thyroid function in juvenile female rats. They observed decrease in T3 and T4 levels and increased TSH levels in thiadiazole copper administrated female rats following a 20-day pubertal female assay.[8]

Unlike vitamins, the presence of multi-minerals in a supplement or food can create adverse reactions, due to the competitive nature of their chemistry. Competitive interactions exist between Cu and Fe. Ceruloplasmin and hephaestinare is Cu-dependent enzymes essential for releasing Fe from certain tissues and involved in the transport of Fe from enterocytes into the circulation, respective. Cu deficiency has been associated with anemia in adults and infants.[9] In addition, excess amounts of Zn also have an antagonistic effect on Cu and Fe in adults.[10]

Iodine

Iodine is a constituent of the thyroid hormones thyroxine (T4) and triiodothyronine (T3) and in that capacity, it takes an interest in the procedures controlling the development of cells and the development of cell fluids. During pregnancy, the demand for iodine is more due to the requirements of developing fetus as well as due to the loss of iodine from mothers milk.[11] Since the excess iodine is expelled from the body, its status can likewise be estimated in urine. The urinary iodine focus parameter is somewhat higher in pregnant ladies (up to 150 mg/l) and its concentration decides infants' birth weight, length, and head boundary.[12]

Iodine is an integral part of the thyroid hormone and has been associated with brain development. Iodine deficiency is the most predominant cause of mental impairment in the world. The exact mechanism of Iodine and its influence on brain development is still unclear, but is thought to begin with genetic expression. Several brain functions and structures are thought to be affected by iodine and thereby thyroid deficiency.[13]

After the thyroid, the ovaries have the second largest reserve of iodine in the body. Iodine deficiency produces changes in the ovarian production of estrogens as well as changes in the estrogen receptors of the breasts. In an iodine-deficient state, ovarian estrogen production increases, while estrogen receptors in the breast increase their sensitivity to estrogen, leading to increase in risk of developing breast cancer.[14]

Iron

Iron homeostasis is maintained by altering the absorption of iron from the gut and the release of iron from storage in hepatocytes and macrophages. A key regulator of these processes is hepcidin. In a recent publication by Xi Huang, a direct mechanism of interaction between estrogens and hepcidin has been demonstrated, where estrogen decreases the expression of hepcidin mRNA.[15] Wyllie and Liehr have investigated the relationship between an elevated dietary iron intake and the incidence of carcinogen-induced mammary cancer in rats and estrogen-induced kidney tumors.[16] Increased levels of iron because of menopause, could be a hazardous factor influencing the well-being of postmenopausal ladies.[17]

Iron has also been found to play a crucial role in the development of insulin resistance. Tuomainen *et al.* have demonstrated the influence of increased body iron stores, as measured by serum ferritin concentration, and its effect on elevated serum insulin, blood glucose, and serum fructosamine concentrations.[18]

Iron and copper are vital supplements assuming important jobs in fertility and health. The type 5 enzyme of acid phosphatase is a Fe-containing molecule found in semen in large quantities and of prostatic origin. It is believed that its presence may be associated with the liquefaction process of semen. Interestingly, increased amounts of this enzyme are connected to a variety of male diseases, especially prostate cancer, which led to its establishment as a clinically useful tumor marker.[19] Infertility is a known complication in males with sickle cell disease, which is usually accompanied by low levels of ferritin. On the other hand, excessive dietary doses result in testicular atrophy, morphological changes in the testes, impaired spermatogenesis, epididymal lesions, and impaired reproductive performance. Males with hemochromatosis tend to have reduced gonadotropin circulation, thereby, leading to decreased testosterone levels.[20]

Manganese

Mn is a component of the dismutase enzyme which is an antioxidant that aids to fight free radicals and can neutralize superoxide ions.

A study conducted by Al-Jeborry demonstrates that women with PCOS had significantly higher serum manganese (mean = 7.3 ± 1.7) than healthy women (mean = 2.2 ± 1.2).[21] This is in contradiction to an earlier finding that serum manganese of PCOS patients was lower in comparison with control. In this study, they clarified that because oxidative stress is increasing in women with PCOS, so that serum manganese value was diminished as a consequence of utilization in antioxidant defense systems which includes MnSOD.[22]

Mn and its interrelation with thyroid hormone regulation are not very well documented. There is recent hypothesis stating that Mn may interfere with deiodinase activity, thus disrupting circulating thyroid hormone concentration. Dopamine is a known inhibitory modulator of thyroid stimulating hormone (TSH) secretion. The contribution of dopamine and dopaminergic receptors in neurodevelopment, just as TSH modulation, has led to the hypothesis that excess of manganese introduction may prompt antagonistic neurodevelopmental results because of the interruption of thyroid homeostasis using the loss of dopaminergic control of TSH. This disturbance may change thyroid hormone levels, bringing about a portion of the shortages related to gestational presentation to manganese.[23]

Mitochondrial dysfunction has been implicated in a number of diseases including neurodegenerative diseases cardiomyopathy and diabetes. There is an extensive body of evidence that supports the hypothesis that MnSOD activity would be beneficial in treating diabetes and its complications. Mn supplementation improves glucose tolerance and insulin secretion as well as increases insulin secretory capacity.[24]

Selenium Se

As a constituent of selenoproteins, selenium has structural and enzymic roles, in the latter context being best-known as an antioxidant and catalyst for the production of active thyroid hormone. Selenoproteins have emerged in recent years as possible biomarkers of several diseases such as diabetes and several forms of cancer. Se deficiency has been linked to retardation of bone development, decreased levels of growth hormone, insulin like growth factor -1 (IGF1) in humans.[25]

The level of Selenium deficiency in ladies results in infertility, premature births, and inability in the maintenance of the placenta. The newly conceived from a selenium-insufficient mother experiences the ill effects of strong weakness. Selenium prerequisites of a pregnant and lactating mother are expanded because of selenium transport to the embryo by means of the placenta and to the newborn baby by means of bosom drain via breast milk.[26]

At present distinguished proof of new selenocysteine-containing proteins has uncovered connections between Se and the hormonal arrangement. A few selenoproteins take an interest in the protection of thyrocytes from damage by H_2O_2 delivered for thyroid hormone biosynthesis. Selenium deficiency has been associated with thyroid conditions like Hashimoto's thyroiditis, a type of hypothyroidism in which the immune system attacks the thyroid gland. The Se content in endocrine tissues (thyroid, adrenals, pituitary, testicles, and ovary) is higher than in numerous different organs. Spermatogenesis relies upon sufficient Se supply, while Se overabundance may hinder ovarian capacity.

Zinc

Zinc plays a major role in the regulation of blood sugar, thyroid and gonadal functions, adrenal hormone and prolactin production, acid-base balance, and calcium metabolism. Zinc has structural roles in biological membranes, cell receptors (for hormones including testosterone) and other proteins. Insulin is stored as a hexamer containing two Zinc ions in β-cells of the pancreas and released into the portal venous system at the time of β-cells de-granulation.[27] Zn ions which are co-secreted with insulin suppress inherent amyloid genic properties of monomeric insulin. showed that high concentrations of glucose and other secretagogues decrease the islet cell labile Zn. Oxidative stress plays an important role in the pathogenesis of diabetes and its complications. Zinc is a structural part of key anti-oxidant enzymes such as superoxide dismutase, the deficiency of which progresses to the development of increased oxidative stress. Studies have shown that diabetes is accompanied by hypozincemia and hyperzincuria.[28]

Zinc is essential for normal levels of thyroid hormones such as triiodothyronine (T3), tetraiodothyronine (T4), and thyroid-stimulating hormone (TSH). Some of the studies showed that zinc deficiency leads to decrease in T3 level. The well-known effect of zinc on some endocrine glands such as pituitary-a master gland and on hypothalamus is that it appears a role in the synthesis of releasing hormones such as thyrotrophic releasing hormone. Some of the studies showed that in hypothyroidism alteration in zinc level. Patients with thyroid cancer have significantly low levels of zinc.[29]

Castro-Magana *et al*. have investigated the relationship of Zn and androgen for growth retardation. Their studies suggest that testosterone plays a critical step in the overall metabolism of Zn. Lower Zn levels have been associated with lower testosterone levels in children and therefore delay in the appearance of secondary sexual characteristics.[30]

CONCLUSION

Trace elements are essential not only as intermediaries in metabolism but also for their potential roles in the production, secretion as well as excretion of various hormones. The application of existing knowledge of the importance of trace elements to problems of human health will depend on a clearer understanding of events that link molecular, biochemical mechanisms to the clinical manifestation of their deficiencies. The recent focus on research has found that the imbalances in the optimum levels of trace elements may adversely affect biological processes and are associated with many fatal diseases. Recently, efforts have been focused to attempt to advance understanding of the relationship between trace elements, and their role in hormone homeostasis. Most available literature focuses on individual trace elements and their impact on one particular endocrine glad. Our manuscript summarizes the interdependence of trace elements and the disorders caused by changes in the homeostasis of various hormones as a result.

Any trace element deficiency (and, in a number of cases, excess) may lead to disease or organ dysfunction depending on their effect on the structure, on body fluids, enzymes, high energy compounds, and so on. However, there is no single formula determining an ideal level of essential trace elements in the human body as requirements for different elements will differ depending on a number of criteria; for example, they will be different for a man or woman (especially if she is pregnant or lactating), for a younger or older person, for people with different body dimensions, and those with certain genetic conditions. Demand for trace elements will also be different during times of active healing processes for wounds or burns, during infections or diseases (anemia, coronary artery, Keshan) or in alcohol abuse. Apart from that, it is important to remember that trace elements react with other components and minerals that may be present in one's diet; (iron versus copper), oxalates (iron), phytates (zinc), fiber (manganese), and polyphenolic compounds (molybdenum). Moreover, geographical location, namely local environment (abounding in or lacking certain elements), food accessibility, or pollution may also have their considerable input in the process as well as some human factors such as local customs, practices and even ethnicity determined by people's adjustment to local environments.

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