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THE INTERPLAY OF OXIDATIVE STRESS ON THYROID HORMONE DISORDERS

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Abstract

Oxidative stress is the comparative glut of free radical and antioxidant produced in an individual. Numerous biological processes of the body leads to the generation of free radicals. Thyroid hormone, an example of the aforementioned act on many organs and tissues to elicit some significant functions which include control of cellular metabolic rate, brain development, muscle function, bone development and maintenance among others. Hyperthyroidism was shown to increase basal metabolic rate which in-turn result in the generation of excessive free radicals since free radical are generated due to metabolic process in the body. However, ambiguity still surround hypothyroidism and it's mechanism in generating free radicals. Hence this review aimed atinvestigat ing the ambiguity and our resultshows that both hyperthyroidism and hypothyroidism increase basal metabolic rate hence rise the oxidative stress. Furthermore, antioxidant supplement like Vitamin E, Vitamin C, β carotene, Selenium can be effectively used in the treatment of treatment of thyroid diseases.

Keywords

Oxidative Stress, Free Radicals, Thyroid Hormone, Basal Metabolic Rate, Antioxidant, Hyperthyroidism, Hypothyroidism.

Introduction

Free radicals are reactive chemical species generated from exogenous, endogenous and respiratory redox reactions in the mitochondria. These substances lead to oxidative damage when these products (reactive oxygen species and free radicals) are produced in excess. However, these effects could be prevented by an antioxidant defensive mechanism comprising enzymatic and nonenzymatic radical scavenging and neutralizing systems [1,2].

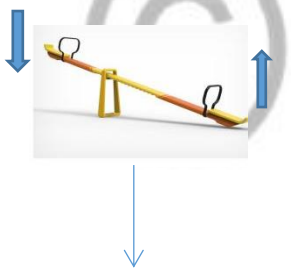

Fig 1: Mechanism responsible for oxidative damage in cells. ADM: Antioxidant defense mechanism, ROS: reactive oxygen species

Several physiological processes of the body also lead to the generation of reactive oxygen species and free radicals, such as aerobic tissue respiration, and the metabolic effect of thyroid hormones [3] e.t.c. The synthesis of triiodothyronine (T3) and thyroxine (T4) catalyzed by thyroid peroxidase (TPO) in thyroid follicles involves the participation of H_2O_2 radicals [9]. Thyroid hormones tend to change the activity and number of

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mitochondrial respiratory chain enzymes, which tends to increase the generation of reactive oxygen species (ROS) [4,5]. There is controversy regarding the association of hypothyroidism with either an increase or decrease in antioxidants [6-7]. Hence, this review aims to investigate the relationship between thyroid hormones and oxidative stress, its implications in health and disease, its remedies, and, most importantly, its mechanism in improving the antioxidant defense system.

Thyroid Hormones and Their Functions

The thyroid hormones tri-iodothyronine (T3) and thyroxine (T4) are produced and released by the thyroid gland through the iodination of a tyrosine residue in thyroglobulin [10]. The synthesis of these hormones is preceded by the release of thyrotropin-releasing hormone (TRH) from the hypothalamus to the anterior pituitary gland and the sequential release of thyroid-stimulating hormone (TSH) from the anterior pituitary gland.

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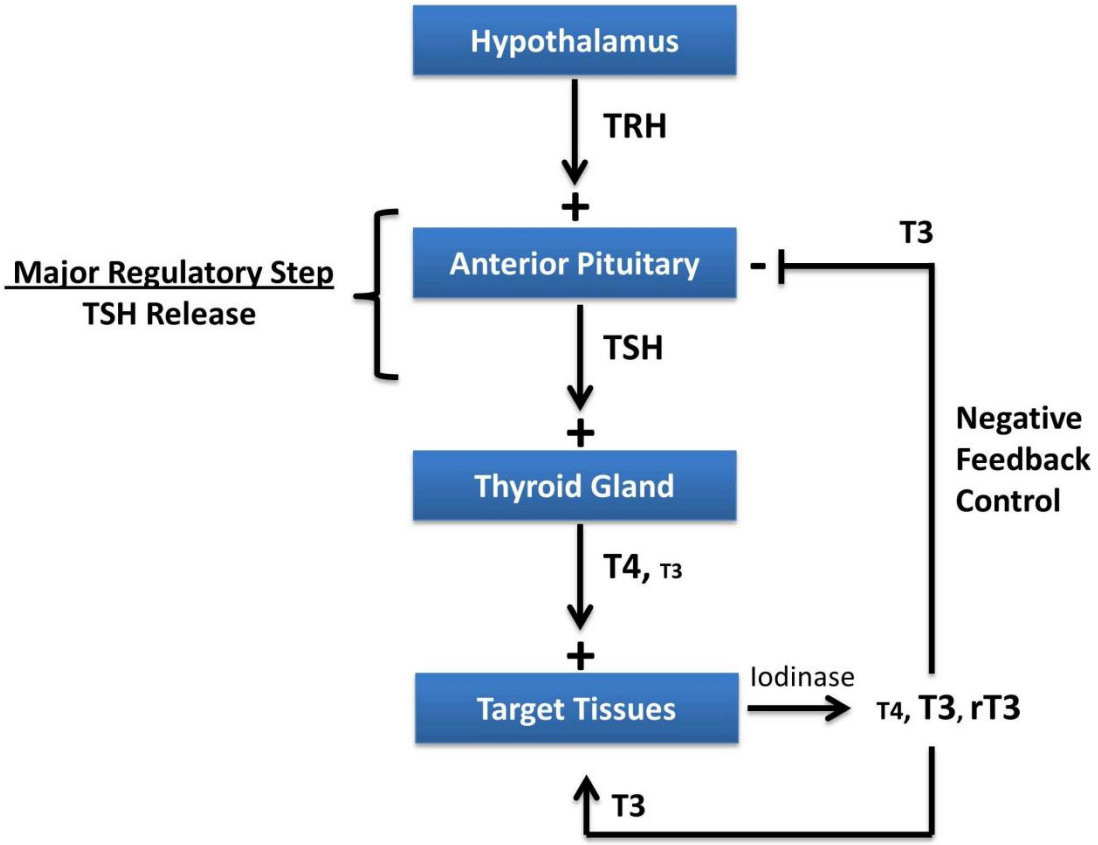

Fig 2: Thyroid Hormone Regulation and Release

Thyroid hormones (THs), including triiodothyronine (T3), are effective regulators of many physiological activities, including digestive and heart function, cellular metabolic rate, brain development, muscle function, and bone development and maintenance [11]. Some of these effects are described below:

The Effect on Bone: Thyroid hormones (THs) are associated with the formation and resorption of bones by inducing osteoblast and osteoclast activities. Additionally, they may act on bone either through a direct action on target cells or through stimulation of growth hormone or insulin-growth factor 1 (IGF-1). Recent studies have shown that T3

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can directly trigger the production of IGF-I in osteoblasts and augment T3 stimulation of proline incorporation, osteocalcin and alkaline phosphatase [12].

The Effect on the Heart: The general effect of THs on the heart causes an increase in beta receptor expression, which leads to increased cardiac output, stroke, volume, contractility and heart rate [13].

Additionally, THs are robust vasodilators of the systemic arteries, which include coronary arteries, and they also have inotropic residences and affect excitation-contraction coupling. [14].

The Role in Brain Development: Thyroid hormones are fundamental for brain function and corporation during life. T3 is implicated in a couple of processes, such as migration neurogenesis, synaptogenesis, myelination and plasticity. Thyroid dysfunction is related to behavioral and neurological issues. The subgranular zone (SGZ) and the subventricular zone (SVZ) of the hippocampal dentate gyrus are the two foremost neurogenic niches that produce new neurons from neural stem cells (NSCs). T3 acts on the SVZ and SGZ at the step where progenitor nerve cells enter the committed step to form mature neurons, thereby triggering progenitor proliferation and differentiation. It was also hypothesized that TH can also have a function on hypothalamus stem cells [15,16]. T3 contributes to psychomotor symptoms in the brain and has an effect on neurodegeneration and cognition [17].

The Effect on Adipose Tissue (fat) and Liver: TH is very important in the function and development of white adipose tissue (WAT) and brown adipose tissue (BAT). Studies have shown that T3 induces intracellular lipid accumulation and various adipocyte-

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specific markers, such as glycerol phosphate dehydrogenase and malic acid enzyme. It also stimulates fat cell cluster formation and adipocyte cell proliferation [18]. T3 may also stimulate lipolysis, which may induce other nuclear hormone receptor systems, thereby promoting cell differentiation [19].

Malic acid is one of the enzymes regulated by TH and has been demonstrated to be stimulated by the direct action of T3 and a secondary effect due to stimulation by other gene products regulated by growth hormone, which is also induced by T3. Malic enzyme is unresponsive to T3 in the brain but sensitive to a hormone in the liver. This suggests that T3-mediated stimulation of malic enzyme transcription is regulated by factors such as insulin, carbohydrate intake and cAMP. It has been viewed that T3 effects on malic enzyme gene transcription are mild in fasted animals but are most pronounced in animals that are fed a sucrose-containing fat-free diet [20].

Metabolism: THs increase the basal metabolic rate and gene expression of Na^+/K^+ ATPase in various tissues, which results in a surge in oxygen consumption, the rate of respiration and body temperature [13]. It also stimulates the metabolism of carbohydrates, anabolism of proteins and catabolism of proteins in high doses. They can also cause gluconeogenesis, increased glucose reabsorption, glucose synthesis, and oxidation [13].

Mechanism of thyroid hormone function

The signaling pathway for actions of thyroid hormones is complex and controlled by the expression of cells with a distinct thyroid hormone transporter (monocarboxylate transporter 8 (MCT8) or other related transporters), activation and deactivation of local

ligands, homologs of thyroid hormone receptors (TRs) and interactions with corepressors and coactivators [21,22]. Additionally, thyroid signals undergo a give and take system with other pathways, such as peroxisome proliferator-activated receptors (PPARα, PPARγ) and liver X receptor (LXR) [23,26].

There are two isoforms of thyroid hormone receptor, TRα and TRβ.

TRα has a T3-binding splice product, TRα1, and non-T_3-binding splice products (TRα2 and TRα3) in addition to their prune forms. TRα1 is predominantly expressed in the brain, heart and skeletal muscle [21]. TRβ also has T3 splice products, which include TRβ1, which is found in many tissues; TRβ2, which can also be found in the brain, retina and inner ears; and TRβ3, which is found in the kidney, liver and lung [21]

Transcriptional activities of T3/TRs; TRs contain a modular functional site, an N-terminal site, a DNA-binding site to acknowledge thyroid hormone responsive elements (TRES), a hinge region and a C-terminal ligand binding site that is responsible for forming dimers with further nuclear receptors [24]. TRs heterodimerize with retinoid X receptor (RXR) and bind to TREs within the promoter regions of desired genes. The TR/RXR heterodimer exhibits the highest T3 binding affinity and remains steady for ligand binding. [25].

In the absence of T3, TRs act as transcriptional repressors, but when they associate with T3, they cause disconnection of their corepressor, hence bringing up the desired gene expression [24].

Oxidative stress and Thyroid Hormone Function

Oxidative Stress

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Oxidative stress is the comparative glut of reactive oxygen species and antioxidants in cells and the ineptitude of a biological system to detoxify these products. These products have been associated with different pathological conditions [27]. An equilibrium phase is required for normal functioning of a biological system [28]. Nature has provided numerous biochemical mechanisms to establish the equilibrium phase in the biological system to avoid the consequences that might come its imbalance.

Physiological role of free radicals

Free radicals are atoms or groups of atoms with an uncoupled number of electrons formed when oxygen interacts with certain molecules. This interaction can lead to a chain reaction that can cause a serious danger to the system [29]. Cellular activities might be reduced or stopped. To prevent this occurrence, the biological system has devised an antioxidant defense system that relates to free radicals to maintain homeostasis [30]. The presence of free radicals in low optimal amounts is required in numerous biological processes, including the following:

Aerobic respiration in the mitochondria

Mitochondria are the highest producer of free radicals, although they are a disadvantage in their self-destruction. Aerobic organisms use mitochondria to maintain their lives by generating energy from adenosine triphosphate through oxidative phosphorylation [31,32].

Respiratory bursts in neutrophils

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Neutrophils constitute the front-line soldiers for organisms against infections and display a prominent role in the innate immune response [33]. When neutrophils coincide with stimuli, ROS are produced. Neutrophil-induced ROS maintain the redox environment and induce an inflammatory response [34].

Beta oxidation of fatty acids in peroxisomes

Peroxisomes have recently been shown to have a high affinity for oxygen consumption, which helps in the β-oxidation of fatty acids and hence the metabolism of fatty acids to generate energy [35]. However, it normally generates an excessive amount of ROS if not neutralized by antioxidants, which can be deleterious to cells [36]. Other physiological functions of free radicals include the processing of xenobiotics.

Physiological role of free radicals in thyroid hormone function (iodine metabolism, organization, and deiodination)

Thyroid hormone is manufactured by the thyroid gland from follicles by iodination of tyrosine residue within thyroglobulin [37]. Thyroid hormones help in development, growth, neural differentiation and metabolism in mammals as well as in amphibian metamorphosis [38,39]. These functions might not be accomplished in thyroid hormone deficiency during development, resulting in neuronal deficiency and growth retardation [40]. Thyroid hormones play a part in oxidative stress in mammals due to their ability to induce reactive oxygen species production, harm antioxidant defense and subject most tissue vulnerable to free radicals [41,42]. The most prevalent reactive oxygen species include molecular reduction oxygen, hydrogen peroxide and hydroxyl radicals [11,46]. The cells have numerous substances capable of hunting free radicals and shielding the cells from this effect. These substances include enzymatic antioxidants (glutathione

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reductase, glutathione peroxidase, catalase and superoxide dismutase) and nonenzymatic antioxidants (vitamin C, vitamin E, β-carotene and flavonoids) [43]. Mitochondria are the home of most oxidative processes and the choice of thyroid hormone target. In thyroid hormone production, oxygenated water is normally produced, which is crucial in iodine intrafollicular oxidation through the help of thyroid peroxidase [44,45]

Iodine Metabolism: Iodine is a micronutrient that is essential for the health of an individual. It can be obtained from food sources such as vegetables and drinking water. Iodine (5 gm) is enough to take an individual through 70 years of age. Iodine is concentrated in the thyroid gland, and the thyroid gland has multiple follicles filled with a viscous substance called colloid (glycoprotein) [47,48]. Iodine metabolism begins with iodine trapping into the follicular cell by an active transport system. This occurs against the concentration gradient by sodium/iodide symporter protein in the basolateral membrane. Thyroglobulin synthesis and secretion is an independent process that begins in the rough endoplasmic reticulum as a peptide unit. The form of a dimer and carbohydrate moieties was added, and then the molecule now moves to the Golgi apparatus. Thyroglobulin functions as a substrate in the synthesis of thyroid, which later migrates to the apical surface of the plasma membrane followed by sodium-independent iodide/chloride transporter (Pendrin), where iodide is then oxidized to iodine [49,50].

Organification and deiodination: Organification is the process of adding iodine into thyroglobulin during thyroid hormone production. This process follows the oxidation of iodide by the enzyme thyroid peroxidase. Iodide attaches to tyrosine to form mono-iodotyrosine or di-iodotyrosine, which later result in T4 or T3. The binding is performed enzymatically. Deiodinases play a significant role in the diversification of the function of

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thyroid hormone signaling, and they are expressed in most organs and tissues and function in aiding the eviction of iodine atoms in thyroid hormone molecule rings. Three diodinases have been identified (DIO1, DIO2 and DIO3) and were found to have similar functions [50]

Relationship between Oxidative Stress and Thyroid Hormones

Thyroid hormones control many physiological processes in the body, including growth, development and metabolism. The metabolic action of thyroid hormones is conveyed in oxygen utilization [51]. T3 is derived from the diodination of T4, which is the active ,form of thyroid hormone although findings show that reverse T3(rT3),3-iodothyroamine (TIAM), 3,5-diodothyronine (T2) may have physiological functions[52]The actions of . T3 resolute on its intracellular concentration, which is fully reliant on its movement across the cell membrane in the presence of iodothyronine, decarboxylase and deaminase [53]Metabolic processes involve the generation of free radicals, and nature has provided . the mechanism through which the free radicals produced will be neutralized using the .antioxidant system Hence, the disparity between the freeradicals and antioxidants produced results in oxidativestress. Reactive ox ygen species/reactive nitrogen species produced as a result of oxidative stress have been implicated to be detrimental to all cellular biomolecules (lipids, carbohydrates, proteins and polynucleotides), and the damage caused can be determined by measuring some biomarkers, including ,malonylaldehyde (MDA-end product of lipid peroxidation) carbonyl or advanced ,oxidation protein product oxidized DNA (8-oxohydroxydeoxyguanosine) and

antioxidant measurement (GH, SOD, flux, GSH) [54]. Inadequacy in the thyroid .hormones produced results in hypothyroidism and hyperthyroidism

Hypothroidismis a circumstance in which the thyroid gland does not generate adequate thyroid hormone. Thyroid hormone deficiency can be categorizedas primary when the thyroid gland is unable to generate an appropriate amount of thyroid hormones, which might be a result of the development of the thyroid gland, destruction of the thyroid gland .and blocking of the signaling pathway The secondary classification is when the hypothalamus ceases to generate adequate thyrotropin-releasing hormone (TRH), which might result from tumors or harm the hypothalamus-pituitary axis impact from other endocrine glands [55]An increase in thyroid stimulating hormone, which is the hallmark . of hypothyroidism, can lead to low-grade inflammation and hence oxidative stress [56]. According to Chakrabarti*et al .* MDA levels were increased in hypothyroidism ,2016 cases, indicating an increase in oxidative stress. Although the MDA level decreased after treatment, the improvement could not be compared to that in euthyroid cases[57,58]. The accumulation of free radicals hinders thyroid peroxidase action, whichin turndisturbs thyroid hormone production and eventually leads to the emergence of hypothyroidism [58].The antioxidant status level in patients with hypothyroidism is modified, which shows the influence of oxidative stress, and there was an improvement in the antioxidant status after the treatment but cannot be compared to the normal individual [59]The . connection between hypothyroidism and oxidative stress drives down the action of the endogenous antioxidant system and therefore leads to oxidative stress.

Hyperthyroidism arises when there is an increase in the production of serum free thyroid hormones that fix on thyroid hormone receptors, and this depends on genetic factors and

environmental factors (iodine availability), among others. Additionally, subclinical hyperthyroidism is defined as a TSH decrease with free T4 and free T3 within the normal range. Overt hyperthyroidism is when TSH decreases with increasing free T4 andfT3. ,Additionally, in secondary hyperthyroidism, TSHf T4 andf T3 all increased[60].

Grave's disease is culpable for most hyperthyroid occurrences. Other root of hyperthyroidism include thyroid autonomy ,(toxic adenoma) subacute thyroiditis, ,Hashimoto's thyroiditis, gestational thyrotoxicosis, postpartum thyroiditis and iodine-induced hyperthyroidism, among others [60]. Hyperthyroidism increases the rate of oxygen utilization of cells, as revealed by an increase in the number of mitochondrial cells, size of mitochondria, number of cristae and progressive deterioration seen in mitochondria [61]. According to research conducted by Mirela *et al*., 2012 on oxidative stress and antioxidants in hypo- and hyperthyroidism, there is asignificant difference in MDA in hyperthyroidism cases when compared with negativecontrols [61,62].This might be a result of an increase in cellular respiration of the target tissues brought about by variation in thyroid hormone production and hence an increase in mitochondrial respiratory activities [62]Carbonyl protein was also found to be higher in the . .hyperthyroid state, indicating oxidative damage to protein [63].In a study conducted by ,.Zamoner et al hyperthyroidism in the developing rat testis was associated with oxidative stress and hyperphosphorylated vimentin accumulation [64]. Biomarkers of oxidative stress were found to be high, indicating that hyperthyroidism is connected to oxidative stress, whereas antioxidant system activities were observed to be reduced despite supplementation with exogenous antioxidants [64]..which is consistent with other studies

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In thyroid cancer, 8-oxodG and 4-hydroxyynonenal (4-HNE) were increased in cancerous thyroid tissue, follicular thyroid calcinoma and capillary thyroid calcinomal, which is indicative of oxidative damage. There is also an increase in antioxidant enzymes such as superoxide dismutase, glutathione reductase and catalase, which is a result of the response to increased oxidative stress [65]Differential thyroid cancer was examined for . oxidative stress through estimation of MDA, and there was a significant increase in the MDA level compared to thenegative control. Additionally, the evaluation of MDA after treatment with radioactive isotopes (RAIs) was performed, and the MDA level was seen to markedly increase [66]. Another study found that total antioxidants were noticeably lower in patients with benign .nodules than in normal patients However, there was a significant decrease in antioxidant levels in thyroid cancer patients when compared to the negative control group [67]. Oxidative stress is distinguished by an increase in oxidative markers, and if not checked, it will affect the antioxidant defense system, which can be reflected by a decrease in antioxidant biomarkers.

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Antioxidant Supplementation in the Treatment of Thyroid Disease

The antioxidant defense system is widely known to protect cells from free radical destruction. They work synergistically with each other to protect organs and the system. The role of antioxidants in the prevention and treatment of disease cannot be overemphasized. An ideal antioxidant must be able to chelate redox metals physiologically both in aqueous medium and membrane domain medium, thereby neutralizing free radicals and affecting gene expression in a positive way. Antioxidants can be from exogenous sources (for example, dietary supplements) or endogenous

sources. However, some exogenous dietary supplements not only destroy free radicals but also synergistically enhance endogenous antioxidants in neutralizing free radicals. The most efficient antioxidant compound is the enzymatic antioxidant [68]. which include glutathione peroxidase, superoxide dismutase, and catalase. The nonenzymatic antioxidant substances include vitamin E, vitamin C, and thiol derivatives, for example, glutathione, lipoic acid, thoiredoxin, amelantonin, carotenoid, etc. [69].

Free radicals have been implicated in a number of diseases, including diabetes, cancer, infertility, and thyroid disease.

Thyroid disease exists primarily in two forms: Grave's disease, which is characterized by the overproduction of thyroid hormone due to overstimulation of the thyroid hormone receptor by thyroid hormone autoantibodies [70], and Hashimoto thyroiditis, which is associated with increased levels of high serum thyroid antibodies and/or anti-thyroid peroxidase and accompanied by hypothyroidism or goiter.

Several studies have proven the effectiveness of antioxidant therapy in treating diseases, such as vitamins, selenium, vitamin C, alpha-lipoic acid, and beta carotene, among others. Antioxidant vitamin (A, C, E) concentrations have been shown to be disturbed in hypo- and hyperthyroidism cases, and the changes were observed to be corrected to normal with the achievement euthyroidism [71]. When hyperthyroidism due to Graves' disease was experimentally treated with antioxidant vitamins (E, C, and beta carotene), selenium, zinc and copper, the symptoms brought by hyperthyroidism were observed to be reduced to a certain level, as seen in patients treated with thyrostatic drugs [72]. In different studies conducted with a combination of thyrostatic medication with antioxidants to treat hypo- and hyperthyroidism, euthyroidism was reached in a shorter time than treatment with

only thyrostatic drugs. This was revealed in the oxidative stress biomarkers [73]. It has been demonstrated in many studies that thyroid cytotoxicity can arise as a result of high intake of iodine. Amiodarone, an iodine-containing drug, has also been shown in many studies to induce thyrotoxicosis. Vitamine E empowers the antioxidant defense system, thereby preventing iodine-induced thyroid-induced thyrotoxicity [74]. Selenium is a micronutrient that produces more than one effect, including antioxidant and anti-inflammatory effects. The thyroid gland has the highest concentration of selenium. Selenium is a component of many enzymes that play crucial roles in thyroid hormone metabolism. This activity is carried out by intensifying those enzymes, thereby reducing the content of hydrogen peroxide and lipid peroxidases produced as a result of thyroid hormone synthesis. In living systems, selenium can be found as selenomethionine, selenocysteine and methyselenocysteine [75]. Selenium supplementation is a possible choice of nutraceutical in the treatment of autoimmune thyroid disease to restore the affected clinical features and biomarkers [76].

In summary, antioxidant supplementation can be effectively used in the treatment of thyroid hormone diseases.

CONCLUSION

Thyroid hormones display a heterogenous effect on humans, which includes their impact on the organism metabolic rate. Numerous studies have shown a relationship between thyroid hormones and oxidative stress. The upshot of hyperthyroidism and hypothyroidism has been shown to intensify endogenous generation of reactive oxygen species, which in turn result in oxidative stress revealed by variation in oxidative stress biomarkers. Antioxidant supplements can be effectively used in the treatment of thyroid

diseases. However, the optimal dose required to elicit its action has not been fully elucidated.

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