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Review Article

Oxidative stress in hypothyroidism

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Abstract

Oxidative stress (OS) has become the most discussed topic, especially in the last two decades due to its association with multiple pathological conditions. Since the discovery of its existence, several biomarkers and anti-oxidants have been identified, yet its association with diseases has not been successfully delineated despite management of the diseases. Experimental hypothyroidism when coupled with other free radical-generating conditions and also being a hypo-metabolic state, attenuates OS up to an extent. Nevertheless, hypothyroidism *per se* has been associated with OS despite several studies refuting its presence. Therefore, OS in hypothyroidism is a controversial topic of worth analysis.

Key words: Anti-oxidants, hypothyroidism, oxidative stress

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INTRODUCTION

Oxidative stress (OS), despite the way its name suggested, is a natural phenomenon in the body. However, for the past two decades or so, OS has gained much importance in the field of research. Now, it has been linked to several disorders such as diabetes, cardiovascular diseases, cancer, neurodegeneration, and aging.[1]

Although its concept dates back to 1950, the term OS came to its frequent use in the late 1970s.[2] In our body, multiple reactions take place to maintain homeostasis, support growth, repair, and prevent diseases. These reactions generate harmful molecules and radicals, known as free radicals, which are capable of altering cellular structure in their vicinity affecting cellular function. Therefore, the natural defense system consisting of anti-oxidant system is acting continuously against free radicals. When the natural balance between the rate of generation of free radicals and action of antioxidants is lost, it results in OS.

OS in majority of studies has been reported to be consistently associated with hypermetabolic states such as hyperthyroidism,[3] as thyroid hormones promote mitochondrial utilization of oxygen and therefore leads to excess generation of free radicals.[4] Hypothyroidism on the contrary is a hypometabolic state due to deficiency of the thyroid hormones. Therefore, one may assume that OS should not be more in hypothyroidism because of reduced utilization of oxygen. Subsequently, there were studies observing the presence of OS in hypothyroidism.

OXIDATIVE STRESS

To start with stress according to the definition in physics, it is an internal force experienced by an object per unit area when an external force is applied. Biologically, it is translated as the internal force experienced by the cell or organ or the organism to maintain homeostasis when subjected to an external stressor which has a broad range such as physical, physiological, environmental, psychological, etc., in the entire lifespan the body of an organism experiences many changes in the form of physiological growth, physiological events such as puberty, pregnancy, etc., reproduction, exposure to

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harmful chemicals, toxins, radiation, sunlight, smoke, excess or deficient nutrients, etc. These changes threaten the preexisting homeostasis at cellular level and body accepts the challenge either by neutralizing the threat or by adapting or by establishment of a new homeostasis. This is achieved by synchronization of various neural, hormonal and enzymatic responses within the body.

A free radical is a molecule with one or more unpaired electrons in its outer orbital. This makes the molecule very unstable because it tends to react with anything in its vicinity to gain one more electron (reduction reaction) or lose its unpaired electron (oxidation reaction) to attain stability.[5] Reactive species are of two types: reactive oxygen species (ROS) and reactive nitrogen species [Table 1]. They can be produced exogenously or endogenously for a cell.

Endogenous reactive species are produced physiologically within the body in reactions such as aerobic respiration in mitochondria, respiratory burst in neutrophils, beta oxidation of fatty acids in peroxisome, and processing of xenobiotics by cytochrome P450 system.[6] Exogenous sources of reactive species are toxins, pollution, cigarette smoke, allergens, drugs such as anticancer drugs, heavy metals, and reaction by radiation exposure.[7]

Since evolution has made us evolve into oxygen-preferring aerobic organisms, many endogenous reactions are naturally centered on oxygen molecule. Therefore, in literature, most of the studies center on ROS. Some characteristics of reactive oxygen derivatives are shown in Table 2.[8]

Metabolically, the cell is involved in various chemical processes such as oxidation, reduction, and nitration, the term OS is defined as the stress that results from either excess production of free radicals or decreased effective concentration of antioxidants or both.[9] Oxidation is a very basic chemical reaction of cells where oxygen is consumed to facilitate mitochondrial oxidative phosphorylation for energy production. In this process, molecular oxygen gets reduced to water molecules. However, an oxygen atom can take up free radical only one at a time. Any delay or fault in this coordination during this step leads to leakage of free radicals to its vicinity. With one-electron reduction, several free radicals and H_2O_2 can be formed.

$O_2 + e^- \rightarrow O_2^{-\bullet}$: Superoxide radical

$O_2 + H_2O \rightarrow HOO^\bullet + OH^-$: Hydroperoxyl radical

$HO_2 + e^- + H \rightarrow H_2O_2$: Hydrogen peroxide

$H_2O_2 + e \rightarrow OH^- + OH^{-\bullet}$: Hydroxyl radical

These free radicals are biologically highly reactive. Therefore, they go on attacking nearby lipid protein and carbohydrate residues to attain electrical neutrality. However, this leads to structural and hence functional damage to nearby molecules inside the cell. The major biological process leading to oxygen-derived superoxide anion (O_2^-) production is the mitochondrial membrane electron transport.[10,11]

To control and reduce the deleterious effects of free radicals, nature has provided human beings with a set of anti-oxidants. Anti-oxidant refers to any substance whose presence, even at low concentrations, delays or inhibits the oxidation of a substrate.[10] In our body, each cell and its vicinity is furnished with various types of anti-oxidants which accept the free radicals and thus protect the cellular architecture from oxidative modification. Anti-oxidants are broadly divided into two types: Enzymatic and nonenzymatic. The most common enzymatic anti-oxidants are superoxide dismutase, glutathione (GSH) peroxidase, catalase, GSH reductase, etc., and common nonenzymatic antioxidants are GSH, Vitamin E, tocopherol, ascorbate, etc. Therefore, leakage or overproduction of free radicals and/or decreased effective concentration of antioxidants can lead to OS.

Table 1: List of major reactive oxygen and nitrogen species

Reactive oxygen species		Reactive nitrogen species	
Superoxide	O_2^-	Nitric oxide	NO^-
Hydroxyl	HO	Nitrogen dioxide	NO_2
Peroxyl	ROO	Nitrous acid	HNO_2
Perhydroxyl radicals	HO_2	Peroxynitrite	$ONOO^-$
Alkoxy	RO	Alkyl peroxynitrite	ROONO
Hydrogen peroxide	H_2O_2		
Singlet oxygen	$^1O_2$		

Table 2: Characteristics of reactive oxygen derivatives

Species	Symbol	Properties
Superoxide anion	$O_2^{-\bullet}$	Good reductant, poor oxidant
Hydroxyl radicals	$HO^\bullet$	Extremely reactive (addition, abstraction, and electron transfer reactions)
Hydrogen peroxide	H_2O_2	Oxidant, but reactions with organic substrates are sluggish. High diffusion capability
Singlet oxygen	$^1O_2$	Powerful oxidizing agent with half-life 10^{-6} s
Perhydroxyl radicals	$HO_2^\bullet$	Stronger oxidant and more lipid soluble than superoxide. May initiate lipid peroxidation
Peroxyl radical	$ROO^\bullet$	Low oxidizing ability relative to $HO^\bullet$, but great diffusibility
Alkoxy radical	$RO^\bullet$	Intermediate in their reactivity with lipid between $ROO^\bullet$ and $HO^\bullet$

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Cellular processes involved in oxygen consumption and oxidative phosphorylation result in increased production of free radicals. Hence, association of OS with hypermetabolic states such as hyperthyroidism[3] is clearly implicated by an increased free radical generation by the mitochondrial respiratory system.[4] However, hypothyroidism being a hypometabolic state does not get supported by the same theory and hence initial observations of OS in hypothyroidism were not given due importance in the discussion section by the respective authors.

HYPOTHYROIDISM

Thyroid disorder is the second most common endocrine disorder, next to diabetes mellitus, in the Indian population.[12] Currently, in our country, the burden of thyroid disorder is around 42 million.[13]

Thyroid hormones control the basal metabolic rate of cells by increasing the basal oxygen consumption. Thyroid hormones also promote the synthesis of mitochondrial cytochromes and the activity of cytochrome oxidases. Therefore, in hypothyroidism, deficiency of thyroid hormones decreases oxygen utilization and hence, leads to hypometabolism. Thyroid hormone deficiency also affects physical and mental growth, development of central nervous system, intermediary metabolism, etc.[14]

Hypothyroidism is the most common disorder of the thyroid gland. Among adults, it is otherwise known as myxedema and in children as cretinism. Hypothyroidism can be primary or secondary based on its source of deficiency. The thyroid gland hypofunction accounts for more than 99.5% of cases (known as primary hypothyroidism) whereas the hypothyroidism resulting from pituitary and hypothalamic dysfunction accounts for the rest 0.5% of the cases. In primary hypothyroidism, thyroid hormones are deficient due to defect in the thyroid gland and hence thyroid-stimulating hormone (TSH) levels are higher than normal. In secondary hypothyroidism, TSH secretion is below normal leading to deficiency of thyroid hormones also. On the other hand, subclinical hypothyroidism is associated with few or no symptoms of hypothyroidism, but TSH value ≥10 μU/mL according to literature.[15] However, subclinical hypothyroidism progresses to overt hypothyroidism in proportion to the initial TSH level and progression is faster with the presence of anti thyro-peroxidase antibodies. Hashimoto thyroiditis is one of the most common causes of primary hypothyroidism. It is a chronic autoimmune thyroiditis in which antibodies against thyroglobulin and thyroid peroxide are formed. These antibodies destroy the thyroid cells, finally leading to hypothyroidism.

The incidence of hypothyroidism in a 1995 survey was estimated to be around 4.1 cases per 1000 women and 0.6 cases per 1000 men per year,[16] and the prevalence was reported to be around 2% among women and 0.2% among men.[17,18] According to a population-based study in Cochin, among the adult population of India, the prevalence of hypothyroidism was around 3.9% and that of subclinical hypothyroidism was around 9.4%. The prevalence was found to be higher in women (11.4%) compared to men (6.2%).[19] Similarly, Hashimoto thyroiditis is more prevalent in females in comparison to males due to certain human leukocyte antigen haplotype restriction.[20]

OXIDATIVE STRESS IN HYPOTHYROIDISM

As discussed before, OS has long been associated with hyperthyroidism in many previous studies because of increased oxygen consumption and increased rate of metabolism leading to generation of free radicals. Hypothyroidism, on the contrary, being a hypometabolic state, would lead to decreased oxygen consumption. Therefore, OS in hypothyroidism deals with entirely a different concept. Moreover, despite few studies reporting the presence of OS in hypothyroidism,[21-24] its occurrence has been denied by others.[25-28] Therefore, OS in hypothyroidism is relatively a controversial topic.

Initial studies involving hypothyroidism did not include OS as the main objective. The level of anti-oxidants was mainly assessed in experimental hypothyroidism[29] or in hyperthyroid patients[30] while comparing its levels with euthyroid and hypothyroid individuals. These reports suggested a decreased antioxidant level in hypothyroidism. In these reports, the rise in antioxidants in hyperthyroidism was deduced as a response to increasing OS. However, the authors did not discuss further about the implications of reduced antioxidant activity in hypothyroidism. A lack of rise in antioxidants was implied as a consequence of reduced OS in hypothyroidism.

Many studies were also conducted to assess the effect of hypothyroidism on OS induced by other primary factors such as endotoxin-induced OS in eyes,[31] experimental burn model,[27] model of ischemia/reperfusion injury,[28] etc. In most of these studies, as the OS was induced by a primary experimental condition, there was a decrease in OS when hypothyroidism was added as a secondary factor. The reason being, introduction of hypothyroidism into the OS model, reduced the generation of free radicals and hence reduced preexisting OS. All these reports strengthened the previous notion that hypothyroidism is associated with decreased OS.

Most reports of OS in hypothyroidism alone were available after 1990.[24,32-37] Oxidized low-density lipoprotein (LDL)

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is a known risk factor for atherosclerosis. Diekman *et al*. showed that LDL from hypothyroid patients is more vulnerable for oxidation,[33] indicating OS. Olinescu *et al*. showed an increase in malondialdehyde (MDA) level in obese hypothyroid women.[32] Resch *et al*. compared the enzymatic and nonenzymatic anti-oxidants, endogenous peroxides, and antibody titer against oxidized LDL receptor.[35] Enzymatic antioxidants were higher whereas nonenzymatic antioxidants were lower in hypothyroid patients compared to controls. They illustrated the presence of OS in hypothyroidism by increased anti-oxidized LDL antibody titer, which was higher than controls. However, they did not find any difference in the levels of endogenous peroxides among controls, hypothyroid, and hyperthyroid patients.[35]

Most of the research works conducted in animal models did not reveal the presence of OS. In a study done in female hypothyroid rabbits, an increased resistance to OS was reported suggesting increased protection against OS.[26] In an experimental set up, Mogulkoc *et al*. showed that both GSH and MDA content in cerebral, hepatic, and cardiac tissues in hypothyroid rats were less than in control rats.[38] Based on peroxide level, they concluded that there is reduced oxidative damage in hypothyroidism. However, the authors overlooked the corresponding decrease in tissue GSH level compared to control rats that was in their study. A reduced GSH level itself is an indicator of OS,[39] as GSH is the most common anti-oxidant molecule that nullifies the free radicals.

One of the drawbacks of animal experiments previously done in hypothyroidism was that the experimental condition period was short, whereas the development of overt hypothyroidism in humans in many cases is a long-term event. However, there are reports from other animal studies suggesting the presence of OS in hypothyroidism. They not only showed increased MDA content, but also this was decreased by Vitamin E supplementation as an anti-oxidant.[22,23]

A report by Dardano *et al*. in 2006 suggested that increased TSH itself may lead to low-grade inflammation and OS.[40] This was an interesting study because raised TSH is a hallmark of primary hypothyroidism. Before entering into a phase of overt hypothyroidism, the body experiences a gradual buildup of TSH and the time period varies among patient to patient depending on genetic-endocrinal-immunological differences. In our studies, we found that TSH level correlates with the degree of lipid peroxidation[41] and marker of inflammation such as ultrasensitive C-reactive protein, indicating a proportionate increase in cardiovascular risk factors.[42] Therefore, an association of increased TSH beyond its physiological limit with increased inflammation and OS is a topic deems pertinent for further exploration.

Coronary artery disease is an important secondary complication in hypothyroidism,[43] and Ox-LDL plays an important role in atherogenesis.[44] In 2007, Sundaram *et al*. verified that the LDL in hypothyroid patients is as vulnerable as that in hyperthyroid patients for oxidation.[45] Hypothyroidism generally is associated with hyperlipidemia which often resembles an atherogenic lipid profile.[46,47] Ensuing OS if associated with hyperlipidemia provides an excellent platform for lipid peroxidation. In our human study, we found a positive correlation between MDA content with various lipid risk factors indicative of atherosclerosis[47] as well as protein glycation.[48] Jain and Palmer have suggested that the protein glycation is facilitated by MDA *per se*[49] by acting as an anchor (Schiff linkage) between sugar and protein moieties. Therefore, the same mechanism can lead to protein glycation in long-term hypothyroidism even at normal glucose level. In our later finding, it was interesting to note that though hypothyroidism is a disease more prevalent in women worldwide, the level of lipid peroxidation and protein glycation was higher in male patients suggesting higher OS in male hypothyroid patients. Likewise, OS is reportedly higher among anti thyroperoxidase antibody (anti-TPO Ab) positive cases compared to anti-TPO Ab-negative cases,[50,51] suggesting increased OS in autoimmune hypothyroidism.

The treatment of hypothyroidism requires exogenous oral supplementation of thyroxine and monitoring of thyroid profile till it gets back to normal level. Thereafter, the dosage is maintained with a yearly checkup of thyroid profile. However, TSH level and hyperlipidemia in hypothyroidism normalize slowly with thyroxine replacement therapy.[52] However, the question is what happens to the level of OS which is associated with hypothyroidism. Baskol *et al*. showed an altered antioxidant status in hypothyroid patients before treatment and its remission after treatment.[24] However, the level of MDA despite decrease was not equivalent to control levels, indicating persistence of OS despite the normalization of thyroid profile. Therefore, OS associated with hypothyroidism requires discrete attention because treatment of overt hypothyroidism is a life-long process which mainly targets the maintenance of thyroid profile within normal range and does not target OS.

APPLICATION

As OS takes longer time to normalize than the thyroid profile, following treatment, further cohorts and clinical

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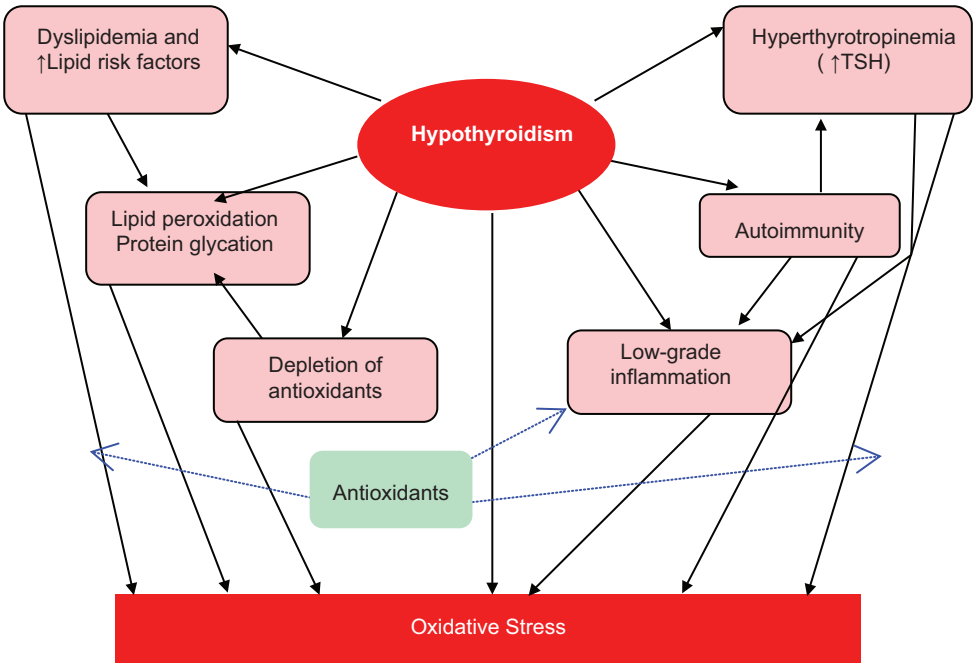

Figure 1: Multiple pathways operating alone or in concurrence leading to oxidative stress in hypothyroidism. Black arrows show the proposed mechanisms and blue arrows represent various proposed targets of anti-oxidants preventing build-up of oxidative stress. Suggested mechanisms of oxidative stress and its probable solution

trials with anti-oxidant supplementation must be carried out alongside traditional treatment in larger group of hypothyroid patients. In addition, the role of genetic polymorphism in hypothyroidism and its relevance in customized therapy and antioxidant trials should also be considered which will benefit the patients at large considering the need of life-long treatment in hypothyroidism.

CONCLUSION

There are controversies regarding the presence of OS in the literature. This review tries to bring together various studies reporting and opposing the presence of OS in hypothyroidism [Figure 1]. OS in hypothyroidism is a multifactorial condition and if not given its due attention may become the linking factor for the comorbidities associated with this disease. In view of extensive studies reporting OS in hypothyroidism along with the presence of atherogenic biochemical profile and cardiovascular risk factors, further cohorts and clinical trials with anti-oxidant supplementation alongside traditional treatment should be undertaken for hypothyroid patients.

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Conflicts of interest

There are no conflicts of interest.

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