Oxidative stress and thyroid pathology

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Summary. The review represents a complex analysis of thyroid disorders mechanisms, involving reactive oxygen species in relation to subcellular distribution of biogenic elements (iodine, copper) with the participation of assign cell targets. Oxidative stress in thyroid gland caused by exogenous or endogenous factors, among them elevated copper accumulation, iodine deficiency as well as its excess amount in non-organification form may lead to various toxic manifestations in thyrocytes, among them lipid peroxidation and proteins carbonylation, DNA strand breaks, caspase- and lysosomal-mediated apoptosis etc. Finally all of these molecular lesions determine of different thyroid diseases progress, cancer included. The review considers a number of issues concerning to how does a tissue defend itself against oxidative stress and beneficial effects of antioxidants in countering the cytotoxicity.
Keywords: thyroid disorders, oxidative stress, iodine, copper, oxidative lesions, cytotoxicity, apoptosis.

Introduction

Epidemiologic studies have documented substantial increases in the frequency of nodular thyroid disease [1]. Nodular thyroid disease is now frequently detected, which reflects its high prevalence in the general population [1] and importance due to possible transformation into thyroid cancer. Moreover thyroid cancer is strongly and consistently associated with goiter [2]. Based on recent data, thyroid cancer is the fifth most common cancer in women [3], and in Italy, it is the second most frequent cancer in women below 45 years of age [4]. Only in few countries (Norway, Sweden) thyroid cancer incidence is decreased [3].

Iodine deficiency disorders cause huge numbers of nodular thyroid disease and become one of the biggest worldwide public health problem of today and are among the most widespread non-infectious human diseases [5, 6]. Their effect is hidden and profoundly affects the quality of human life. Lack of iodine leads to disorders of the reproductive system, brain damage and mental retardation, endemic goiter etc. and the last one dominates among iodine deficiency pathology. According to the WHO endemic goiter affects about 7% of the world population [5, http://www.who.int/gho]. Iodine deficiency thyroid pathology has miscellaneous origin as a result of a complex interaction of endogenous and exogenous factors and arises in the setting of high level of «nonspecific» goitrogens, among them copper, in the environment [7].

The role of reactive oxygen species (ROS) as causes of or as part of causal chain in human disease is vast and has been under extensive study, extending from almost the entirety of the pre-

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vious century into this one [8]. Since first time of ROS mentioned in review article (1945), the use of ROS as keyword in Pubmed search resulted in more than 117.000 articles. Most studies have associated ROS to cancer, diabetes mellitus, cardiovascular diseases, atherosclerosis, aging and so on, less of them to different physiological processes and cellular protective mechanisms that the living organisms use for their survival [8]. Nevertheless thyroid gland tissue has its own particular metabolism because thyrocytes even normal produce hydrogen peroxide (H_2O_2) which is needed to oxidation and organification of iodine [9] little is known concerning of oxidative stress in thyroid pathology progress regarding iodine status, and the available data are scarce and controversial.

Oxidative stress can arise from overexpression of ROS [10]. ROS mostly originate from mitochondria [11]. The rate of ROS production and the activity of the radical-eliminating systems depend on endo- and exogenous factors and vary according to diverse factors ranging from energetic demand of the cell to the expression rate of specific genes [12]. Thyroid hormones play a significant role in ROS production due to their capacity to accelerate the basal metabolism and change respiratory rate in mitochondria [12]. When the antioxidant-prooxidant systems become unbalanced a shift in the intracellular redox balance towards a more oxidizing state, may result in direct oxidative damage to DNA, proteins, cell membrane lipids with the possibility to cause disease. In addition, ROS can stimulate signal transduction pathways and lead to activation of key transcription factors such as Nrf2 and NF-kB. The resultant altered gene expression patterns evoked by ROS contribute to the carcinogenesis process [8].

Reviewing the most data on the subject, this study aims at presenting recent studies that examine the roles play by ROS in human thyroid pathology progress with special emphasis on the balance between antioxidant defense system activity and oxidative lesions depends on trace elements (iodine and copper) supply.

Thyroid function and ROS Production

ROS include any species capable of independent existence, containing one or more unpaired electrons, which are called free radicals and a number of reactive molecules derived from either oxygen. Among them peroxide radicals (O_2^{2-}), hydrogen peroxide (H_2O_2), superoxide-anion radical (O_2^{-}), lipid peroxil ($LOO^{\cdot}$) and the most toxic, singlet oxygen ($^1O_2$) and hydroxyl radicals ($^{\cdot}OH$) [8, 12]. They are formed predominantly in the mitochondrial electron transport chain, cytosol, lysosomes, peroxisomes, plasma membranes belong to endogenous sources of ROS production. The ROS are produced by other pathways as well, including the respiratory burst taking place in activated phagocytes and as byproducts of several cellular enzymes including NADPH oxidases, xanthine oxidase, and uncoupled endothelial nitric oxide synthase [11]. ROS are also generated by exogenous sources include environmental agents, pharmaceuticals, industrial chemicals, ionization radiation etc. [13].

The plasma membranes of the thyroid cells consist of an H_2O_2 generation system in which H_2O_2 production is used for biosynthesis of thyroid hormones [14]. H_2O_2 is produced in the thyroid gland by two isoform enzymes, dual oxidase 1 (DUOX1) and 2 (DUOX2), belonging to NADPH oxidases family, with the most convincing experimental evidence found for DUOX2 [15]. H_2O_2 acts as an electron acceptor at each step of thyroid hormone synthesis, namely at iodide oxidation and, next, at its organification, as well as at coupling reaction of iodotyrosines [14]. It is essential for activity of thyroperoxidase — the key enzyme for thyroid hormone synthesis [15]. H_2O_2 is produced in large excess compared with the amounts of iodide incorporated into proteins. This may be necessary owing to the relatively high Michaelis-Menten constant of thyroperoxidase for H_2O_2 [16]. It is interesting that iodide leakage, presumably the iodide channel that releases iodide at the apical membrane, is acutely regulated by the same cascades and with the same timing as H_2O_2 generation [17]. Under physiological condition the thyroid cell requires the generation of H_2O_2 by DUOXs and not O_2^{-} as for other oxygen species [15].

H_2O_2 generation in the thyroid is quantitatively important, especially in stimulated cells. For example, stimulated dog thyroid slices and FRTL5 and PCCl3 rat thyroid cell lines produce around 6, pig thyroid slices and thyroid cells in primary cultures around 10, and human leukocytes around 17 nmol H_2O_2 / (10 min×10 μg DNA) [16]. However, although an activated leukocyte lives a few hours, the life of the thyrocyte in human adult is seven years [18]. Large quantities and membrane permeable nature of H_2O_2 can lead to its diffusion from the luminal side of the apical membrane back to the cell. Because iron is present in thyroperoxidase and H_2O_2 is indis-

pensable for thyroperoxidase activity, the thyroid gland may be exposed to excessive amounts of either iron (II) or H_2O_2, or both, creating favorable conditions for additional Fenton reaction and, consequently, oxidative damage. Nevertheless, the thyroid cells have affected to constant high level of ROS and should adapt to them, H_2O_2 exhibits the same toxicity for thyrocytes as on other cell types. In thyrocytes of different species, among them human, H_2O_2 at concentrations of less than 0.1 mM induces DNA single-strand breaks [19] and when concentration of H_2O_2 increases (0.1 mM and above), DNA double-strand breaks and apoptosis in thyroid cells are appears, and at even higher levels (above 0.4 mM), necrosis [20], an effect that is potentiated by selenium deprivation and consequent GSH peroxidase depletion. Specific anatomical feature of the thyroid gland, a monolayer of thyrocytes surrounding the thyroid colloid, does separate the colloid from the circulation, avoiding the leakage of ROS into the blood and thereafter to other tissues [21].

Iodine and modulators of its metabolism

Iodine is a crucial component in the formation of thyroid hormone. Considerable evidence indicates that iodine *per se* can ameliorate physiopathology of several organs that take up iodine, primarily the thyroid, mammary and prostate glands and potentially the pancreas, gastric and nervous systems. It is estimated that 2 billion people have iodine deficiency in the world and public health policies have been established to supply deficient populations with the necessary amount of this element in order to eradicate the iodine deficiency diseases, i.e. endemic goiter and cretinism [www.who.int]. Similar to iodine deficiency disorders, excessive iodine intake has also received substantial attention.

Environmental agents, among them copper, can modulate iodine accumulation in thyrocytes as well as ROS metabolism in thyrocytes by metabolism to primary radical intermediates or by activating endogenous sources of ROS. Copper is essential micronutrient for humans and animals, but its excess amount in the body can be toxic and could disturb metabolic pathways [8]. It has been shown that deiodinases *Dio3* was significantly upregulated and *Dio2* downregulated in the frog with completion metamorphosis by copper in the range of 6.4, 32 and 64 μg L^{-1}. Since, *Dio3* inactivates T_4 and T_3, increasing levels of *Dio3* expression and decreasing levels of *Dio2* expression would cause decreased thyroid hormone concentrations in target tissues [22]. Moreover, copper exposure also affects adversely thyroid hormone receptor TRβ expression and could cause follicular hyperplasia. Obviously copper delayed metamorphosis by inhibiting TRβ expression, and copper might have the endocrine-disrupting effect [22].

Copper toxicity in the cell primary is associated with its participation as a catalyst in the Fenton reaction which via reactive oxygen species are produced in huge amounts, and also oxidation of thiol groups of proteins to form disulfide cross-links leading to the loss of their activity [8]. We have shown that in patients with iodine deficiency nodular thyroid goiter excess of copper in the nodular-affected tissue was partly accumulated in metal-binding, stress-related proteins metallothioneins [23]. Moreover, metallothioneins binding ability against copper in the nodule was lesser than in paranodular tissue [24]. Also copper content increased up to twice in non-bound with metallothioneins, labile cell, potentially toxic form. It was in a good correlation with prominent oxidative lesions in thyroid gland reproduced as imbalance of superoxide dismutase (SOD) / catalase system, oxyradicals expression, lipid peroxidation (evaluated as TBA-reactive substance) and thiol oxidation (measure as elevation of GSSG) [25]. People with thyroid nodular goiter had higher activity of asparthyl protease cathepsin D belongs to the mediators of IFN-γ and TNF-α-induced lysosomal path of programmed cell death [26]. This was consistent with an increase of total copper level ($r=0.63$, $p<0.01$) as well as in unbound with metallothioneins form ($r=0.67$, $p<0.01$) in the node tissue. Obviously copper is stored in lysosomes causes their swelling, activation of calcium-dependent phospholipase A2 [27] and determines of higher permeabilisation of lysosomal membranes. This is followed by *in vivo* release of enzymes from lysosomes and designates of the activation of caspases, DNA fragmentation and apoptosis. Thus a high level of copper in the environment contributes to thyroid pathology progress through enhances of metal bioaccumulation in the tissue and consequent oxidative stress and apoptosis activation.

Several studies have shown iodine to be a potent antioxidant [28]. In the brown algae *Laminaria*, which contains a 300.000-fold greater iodine concentration than any other living organism, the inorganic iodine acts as an antioxidant, neutralizing hydrogen peroxide in a two-step process, by converting it first to hypoiodous acid and then to water, thereby preventing formation of a hydroxyl radical [29]. Micromolar amounts

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of I^- decrease damage by free oxygen radicals, increase the total antioxidant status in human serum [30], and defend brain cells in rats from lipid peroxidation [31]. Thyroxine and other iodothyronines act as antioxidants and inhibitors of lipid peroxidation after they are oxidized by hemoglobin and their iodine is released [32]. I_2 supplements decrease lipid peroxidation in normal and tumoral mammary tissues from rats with methylnitrosourea-induced mammary cancer, and prevent the cardiac damage induced by the antineoplastic agent doxorubicin when I_2 (0.05% in drinking water) is administered 2 days before starting the antineoplastic treatment [33]. I_2 exerts a 10- or 50-fold greater antioxidant action than ascorbic acid or KI, respectively. Although the specific mechanisms involved in the antioxidant effect of iodine have not been analyzed in depth, several studies show that I^-could be acting directly as an electron donor that quenches free radicals such as $OH^{\bullet}$ or H_2O_2; alternatively, it may act as a free radical that readily iodinates tyrosine, histidine, and double bonds of some polyunsaturated fatty acids in cellular membranes, making them less reactive with oxyradicals [34].

Low iodine level linked to the increased production of ROS. It has been shown a higher mRNA expression for the extra cellular SOD-3 isoform and increased total SOD enzyme activity in the thyroid exposed to iodine deficiency compared to normal diet [35]. Moreover, two peroxiredoxins (i.e. PRDX3 and PRDX5) that have been connected to H_2O_2 detoxification [36] show increased mRNA expression at 8 weeks of iodine-deficient diet. It should be speculate that increased thyrotropin (TSH) sensitivity as a result of a higher receptor expression could induce thyroid adaptation to iodine deficiency, reduce oxidative stress and consequently normalize gene expression of antioxidant enzymes [35]. Goitrous children had relatively lower enzymatic antioxidant and selenium status as well as endemic goiter tissue contains significantly lower SOD activity and concentration compared to normal thyroid tissue, and the SOD protein does not differ from the normal. They found the same lower SOD activity in patients previously treated with iodized oil injection and hence concluded that there is a deficiency of SOD in endemic goiter tissue, which may cause more prolonged exposure to oxygen free radicals possibly contributing the degenerative changes of the tissue [34].

In general terms, the molecular lesions, such as DNA strand breaks, increases under iodine deficiency. It was shown a significant increase of uracile and oxidized purine/pyrimidine adducts in thyroid DNA under low iodine diet. The increase of uracile modifications under iodine restriction could be an explanation for the high frequency of C → T base changes in TSH receptor mutations that are found in autonomous functioning thyroid nodules (AFTN) in iodine-deficient areas [35].

Contrariwise not only iodine deficiency should cause deleterious effect on thyroid gland. Comparatively the same effect has the excess amount of iodine. Excess iodine permits formation of iodotyrosines, but inhibits hormonogenesis by tying up the TPO-iodination species and diverting it from further iodination of iodotyrosyls to form thyroid hormones [9].

It has been shown that iodide increased oxidative stress in cultured thyroid cells as evidenced by increased intra-cellular reactive oxygen species and lipid peroxidation [37]. The authors suggested that I_2, the molecular form of ionic iodide, is highly reactive with protein, lipids, and nucleic acids and that generation of iodine-compounds may disrupt cellular membrane functions, increase reactive oxygen species, and cause programmed cell death in thyroid cells. The reactive species accounted tyrosine free radical (Tyr•), diiodotyrosyl residue radical (DIT•), diiodotyrosyl residue radical in thyroglobulin (Tg-DIT•), iodine radical (I•), iodinium ion (I^+), hypoiodous acid intermediate [IO- (IOH)], and ascorbate radical (Asc•) [38]. The oxidative state may also be directly involved in Sodium Iodide Symporter (NIS) responses to I^-excess, because a balanced cell oxidation level is critical for a normal functioning of gene expression machineries at the pre- and posttranscriptional levels [39].

Iodine excess could dose dependently induce hepatic steatosis in BaLB/c mice agreement with oxidative stress represented by oppression of glutathione peroxidase and superoxide dismutase and arise of malondialdehyde level [40] and as a after-effect response apoptosis pathway activation [37]. Also in mice and rats hepatic deiodinase D1 activity and gene expression was decreased under excess iodine intake [40, 41]. Moreover, excess of iodine ((3000 or 6000 μg/L) for 8 weeks) increase thyroid hormones, lipid peroxides, and antioxidants (catalase, SOD enzymes, and total antioxidants) in euthyroid and hypothyroid rats [41].

It has been shown that hyperplastic thyroid epithelium under iodine deficiency nodular colloidal goiter sacrificed its ability for iodine organification and therefore increased of level of

inorganic iodine [23, 24]. This pattern fell into line with higher copper level (r=0.69, p<0.01), manifestation of oxidative damage (increased of SOD, catalase and glutathione trasferase (GST) activity (r=0.73, r=0.59 and r=0.64 correspondingly, p<0.01), metallothioneins level (r=0.97, p<0.001) and cytotoxicity (increased of DNA fragmentation, r=0.51, p<0.01) in nodule-affected part of thyroid gland [25]. Therefore it can be assumed that under deprivation of iodine organification surplus of inorganic iodine has been created in human thyroid gland and determined formation of iodine toxic intermediates in hyperplastic thyrocytes after iodine oxidation by thyroperoxidase. This scenario a stimulating effect on the antioxidant defense system was proved. Quite similar results, as increased of lipofuscin level, lipid peroxidation, necrosis of human epithelial cells, and destabilization of mitochondrial membranes as well as development of autoimmune processes in the tissue of thyroid gland were obtained after iodine administration in micromolar range into human body [42].

Case in point high I^- treatment increased ROS production, modulates mRNA expression of *TxnRd1*, *TxnRd2*, and *Gpx2* mRNA and selenoproteins in thyroid cells [39]. Increased ROS levels induced not only *TxnRd* mRNA levels but, more importantly, also TxnRd activity. TxnRd, together with Txn and NADPH compose a highly conserved system (the Txn system) that regulates a variety of intracellular processes such as DNA synthesis, protein-DNA interactions, gene expression, and cellular growth, and it has been described as one of the main effectors of ROS responses [43]. In addition, high Txnrd1 expression and activity have been directly connected with cellular protection against oxidative stress induced by 4-hydroxynonenal, one of the end products of lipid peroxidation [44].

Thyroid Hormones, Metabolism, and ROS Production

Thyroid hormones regulate oxidative metabolism and thus play an important role in ROS production due to their known effects on stimulation of the elements synthesis of the respiratory chain, which further enhances the reductive state and, potentially, express ROS [45]. Finally, the increase in thyroid hormones levels has been shown to modify the composition of membrane phospholipids leading to oxidative damage to them, particularly to the mitochondrial one [46].

In hypothyroidism, a decrease in free radical production is expected because of the metabolic suppression brought about by the decrement in thyroid hormone levels [47]. The effect of hypothyroidism on the antioxidant enzymes has been investigated in several tissues, but the results are rather controversial and the response of the antioxidant enzymes to hypothyroidism within a single tissue is not always similar [48]. There are several reports declared that hypothyroidism and Hashimoto's thyroiditis were associated with increased production of ROS and, in turn, oxidative lesions of cell's compartments assessed by elevated lipid peroxidation [49]. Additionally, it was shown that hypothyroid patients had a deficient anti-oxidant defense system in the form of decreased activity of SOD, level of ferric reducing ability of plasma, GSH and increased of nitrite level and myeloperoxidase activity [50]. Moreover, thyroidectomy or thyroparathyroidectomy were shown to be associated with oxidative stress, elevation of levels of nitric oxide and malondialdehyde, and oppression of catalase, decreased despite the application of replacement therapies [51]. Case in point total oxidant status and oxidative stress index were higher, and total antioxidant status and total thiol levels were lower in the overt hypothyroid group compared to euthyroid and subclinical hypothyroid subgroups among Hashimoto's thyroiditis patients [52]. The fall in GSH levels coincided with a marked elevation of GPx activities in Hashimoto's thyroiditis patients. Moreover, it has been reported that oxidative stress is slightly but significantly elevated in hypothyroid patients with positive antithyroperoxidase antibody (TPO-AB) compared to negative TPO-AB matched controls and also GSH levels are in a good inversely correlation with TPO-AB titers as well as TSH activities [53]. It is expected that patients with Hashimoto's thyroiditis who have normal levels of thyroid hormone have a significantly higher thyroid cancer risk than those who are hypothyroid [54] possibly due to permanent oxidative stress occurred in cells.

On the other hand, hyperthyroidism is characterized by an increasing cellular metabolic rate, and thus an increase amount of free radicals [55], peroxides levels, reduce the levels of protein adducts etc. It has been shown an increased rate of NADPH-supported generation of superoxide radical by microsomal fractions from rat liver after 2 (30%) to 7 (67%) days of treatment of euthyroid rats with T_3 [56]. This was in agreement with concomitant elevation in microsomal NADPH oxidase activity, which has been shown

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to be associated with O_2^- production [57]. Redox imbalance due to hyperthyroidism induces adaptation of antioxidant systems spill over into either an increase or a decrease in antioxidant enzymes, inducing ERK1/2 activation [58]. Several examples justify mentioned above. In a recent study, where total anti-oxidant capacity and total oxidative stress were studied in patients with hyperthyroidism, serum total anti-oxidant capacity was found to be significantly lower, while serum total oxidative stress levels were significantly higher in hyperthyroid patients. Also, serum total anti-oxidant capacity and total oxidative stress levels were observed to be correlated with TSH, FT_3, and FT_4 levels in these patients [59]. Additionally the patients with hyperthyroidism had increased levels of malondialdehyde and myeloperoxidase activity in comparison with the controls [50]. Treatment with propylthiouracil attenuated these increments after one month [50].

There is evidence that ROS might contribute to the pathogenesis of Graves ophthalmopathy. The complex evaluation of the antioxidant state in untreated Graves' hyperthyroidism has shown significantly increased activity of intracellular ROS scavenging enzymes: SOD, catalase and GPx, compared to healthy subjects [60]. On the contrary, it has been reported only that patients with newly diagnosed Graves' hyperthyroidism have reduced erythrocyte SOD activity [61] as well as reduced vitamin E and coenzyme Q plasma levels [62]. In a study, oxidative stress profile was investigated in patients with Graves ophthalmopathy before and after normalization of thyroid hormones. Although the values of ROS decreased and levels of antioxidants got corrected significantly after anti-thyroid treatment, oxidative stress levels remained significantly elevated as compared to normal persons [63].

Although nodular lesions are frequent in the overall population, only 5-10% of thyroid nodules correspond to malignant lesions, and thyroid carcinoma is a rare disease that accounts for just 1% of all human cancers, although it is the most common endocrine malignancy [64]. Primary cell transformation and malignant cancer development is frequently characterized by increased oxidative stress that induces mutations and increases growth signaling. The data extracted from Oncoming database suggested increased NOX1-5 gene expression that, as part of NADPH oxidase complex, induces O_2^- production and reduced expression of genes coding for enzymes that remove oxygen radicals from the tissue environment. The only exceptions were increased expression of mitochondrial SOD2, GPX1, and GPX2 thus highlighting the importance of mitochondrial activity in tumorogenesis [65]. In thyroid adenomas a marginal decrease in SOD activity points to the possible involvement of accumulated superoxide radicals in the resultant higher lipid peroxidation levels observed. In contrast to the adenomas, an increase in SOD activity was found to occur in thyroid carcinomas. This may lead to production of higher amounts of H_2O_2, which has been shown to be true in many human tumor cells [66]. In spite of elevated catalase in follicular carcinomas as well as GPx in both types of carcinomas, an increase in lipid peroxidation occurred. The new findings of higher AMPK activation in human papillary thyroid cancer in relation to benign lesions and the possibility that this pathway modulate cell growth, apoptosis and survival raises several questions that need to be answered in order to better define whether AMPK could be a novel target in thyroid cancer patients. The differentiated papillary thyroid cancer is indolent and most of these tumors do not present an aggressive behavior [67].

The excess amount of free radicals and/or oxidative stress, resulting in the numbers of molecular and genetic disorders could be backgrounded for mechanisms of wide range of disorders development. As we have shown above the response of oxidative stress system is well-studied under hypo- and hyperthyroidism and particularly under thyroid carcinogenesis. But in the same time data connecting to oxidative stress parameters in human goitrous thyroid gland are scarce and controversial. Only 24 papers have information about «euthyroid, oxidative, pathology» and 146 papers have information connected to «euthyroid, oxidative» in the PubMed annotation. This lack of knowledge should complicate of our understanding of mechanism of possible thyroid goiter transformation mainly in cancer as well as findings of markers of early-warning system of thyroid cancerogenesis. For instance, by one side some reports have justified that accumulation of ROS in the thyroid gland within the age causes increased expression of intercellular adhesion molecule 1 (ICAM-1) on thyrocytes which have a key role in the onset of inflammatory responses [68]. By the other side iodine deficient goiters showed extensive presence and typical arrangement of dendritic cells which are positive for ICAM-1 [69] and ICAM-1 has been found to be up-regulated in

many human cancers, among them thyroid [70]. But up to now there are no studies about connection between oxidative lesions in goiter hypertrophic thyrocytes and ICAM-1.

A recent study suggested that the expression of NFE2L2 target genes were increased accompanied by decreased expression of wild type *KEAP1* in the thyroid multinodular goiter tissues obtained from the proband [71]. The KEAP1-NFE2L2 regulatory pathway is a major biological defense system against oxidative damage [72]. Notably, somatic mutations that stabilize NFE2L2, thus conferring protection against oxidative stress, have been identified in *KEAP1* in human cancers [72].

In one study, euthyroid multinodular goitrous as well as non-malignant thyroid tumors patients were found to be associated with undisturbed oxidative status and prooxidant-antioxidant balance whilst in malignant tumors the balance was altered, and the change observed in the lipid peroxidation, SOD and GPx [73]. Also it has been shown that lipid peroxidation, evaluated by 4-HNE method, was increased in nodular goiter. The increased of oxidative stress in goitrous thyrocytes is probably attributable to the accumulation of H_2O_2 after thyroperoxidase blockade, or associated with the lack of iodine [74].

Our previous data indicated that thyroid gland tissue of patients with euthyroid nodular goiter was characterized by lower Mn-SOD and GST activity and also redox index of glutathione, meanwhile by higher levels of catalase activity and glutathione than in normal tissue [23, 24, 25]. Moreover several oxidative lesions in affected thyroid gland were indicated. Among them higher level of lipid peroxidation, oxyradicals and oxidized glutathione, compared with the correspondent control [24, 25]. The integrative index of oxidative stress has been justified total suppression of antioxidant defense in thyroid goitrous tissue compare with normal one (=-0.61) [75].

More strict results obtained under comparison of human nodular thyroid tissue and unaffected contralateral part of gland. It has been shown the coherent activation of SOD, catalase and GST, decrease of GSH level and increase of level of cysteine-reach metal-keeping and stress-responsive low-molecular weight proteins named metallothioneins (both MT-SH and MT-Me) in affected part of thyroid gland. Higher level of oxyradicals and GSSG has been also detected in this part. Goitrous thyroid tissue has been highlighted the signs of cytotoxicity, among them higher free cathepsin D activity and higher level of DNA strand breaks in node, as well as activation of glycolysis compare with contralateral part of human thyroid gland [23, 24]. The accumulation of ROS ($r=0.72$, $p<0.01$) and initiation of oxidative stress in the cell could be the reason for shifting of energy balance to anaerobiosis [76]. In paranodular tissue range of indices variability as comparing with parenchyma of contralateral part was lesser than in node, but had the same trend in general. Thus, we should assume about exhaustion of compensatory capability of hypertrophied thyrocytes in the node compared to paranodular tissue despite of some compensatory changes in stress-response systems.

Metallothioneins overexpression is frequently observed in various malignancies and in some cases increased with growing malignancy grade of those tumors. Lines of evidence suggest, that metallothioneins may diminish the suppressor function of the p53 protein leading to uncontrolled growth and proliferation [76]. At the same time not to much attention pays for evaluation of the role of metallothioneins under thyroid pathology. The most recent study indicates that a possible role of metallothioneins as a tumor suppressor in papillary thyroid cancer [77] and them participation into distribution of metals, thereby optimizing the function of thyroid gland [75]. Also under thyroid nodular goiter metallothioneins function is related to scavenge of oxyradicals [24, 25]. Semblable abilities to scavenge superoxide radicals were shown by N-acetyl-cysteine and after-effect deep intracellular ROS decreased to very low levels is associated with decreased DUOXs, thyroperoxidase, tyroglobulin, and pendrin expressions, but not NIS mRNA expression. Such effects on DUOXs expression were also observed *in vivo* [74].

Conclusions. The results, obtained in humans and in animal models, suggest that oxidative damage in the thyroid gland is accompanied by increased oxidative lesions and decreased or increased activities/levels of antioxidants. The thyroid gland has perfectly developed a kind of autoregulation in terms of keeping redox balance under physiological conditions, but after exceeding of adaptive range of tolerance misbalance of antioxidant/prooxidant systems has overcame, huge supplier of oxidative lesions accumulates and pathological changes penetrate. Prooxidative changes may occur in some cases, like in the presence of redox-active metal ions, among them copper or non-organification iodine.

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Окисний стрес та тиреоїдна патологія

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Резюме. В огляді представлено комплексний аналіз механізмів розвитку тиреоїдної патології за участю активних форм оксигену у взаємозв'язку із субклітинним розподілом біогенних елементів (йоду та купруму) за участю специфічних клітинних мішеней. Окисний стрес у щитоподібній залозі викликається низкою ендогенних та екзогенних чинників, у тому числі посиленням акумуляції купруму, дефіцитом та/або надлишком йоду в неорганіфікованій формі, та може призводити до токсичних проявів у тиреоцитах, зокрема пероксидації ліпідів і карбонилювання протеїнів, фрагментації ДНК, каспазо- та лізосомально-опосередкованого апоптозу тощо. Молекулярні ушкодження визначають ступінь прогресування тиреоїдної патології, включаючи й рак. В огляді розглядаються питання, яким чином тканина захищає себе від окисного стресу, та переваги впливу антиоксидантів у зменшенні цитотоксичності.

Ключові слова: розлади тиреоїдної системи, окисний стрес, йод, купрум, продукти окисної деструкції, цитотоксичність, апоптоз.

Окислительный стресс и тиреоидная патология

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Резюме. В обзоре представлен комплексный анализ механизмов развития тиреоидной патологии с участием активных форм кислорода во взаимосвязи с субклеточным распределением биогенных элементов (йода и меди) с участием специфических клеточных мишеней. Окислительный стресс в щитовидной железе вызывается рядом эндогенных и экзогенных факторов, в том числе усилением аккумуляции меди, дефицитом и/или избытком йода в неорганифицированной форме, и может приводить к токсическим проявлениям в тиреоцитах, в том числе перекисному окислению липидов и карбонилированию белков, фрагментации ДНК, каспазо- и лизосомально-опосредованному апоптозу и т.п. Молекулярные повреждения определяют степень прогрессирования тиреоидной патологии, включая рак. В обзоре рассматриваются вопросы, каким образом ткань защищает себя от окислительного стресса и преимущества влияния антиоксидантов в уменьшении цитотоксичности.

Ключевые слова: расстройства тиреоидной системы, окислительный стресс, йод, медь, продукты окислительной деструкции, цитотоксичность, апоптоз.