Antioxidants and Thyroid disorders

SANJAY AGRAWAL

Introduction

It is well known that oxidative stress (OS), defined as an imbalance between radicals and antioxidant defense, is implicated as a pathophysiological mechanism of different diseases and is a topic of growing interest. Cell injury is a consequence of OS; recognized targets are DNA, lipids and proteins, which react with hydroxyl radicals to form specific products[1]. Especially in the field of cardiovascular diseases, the role of OS has been revaluated[2], even if the therapeutic aftermath is still debated. Antioxidant defenses include enzymatic and non-enzymatic molecules and they are modulated by hormones, which regulate their synthesis and turnover as previously reviewed[3]. CoQ10 is a lipophilic antioxidant, with a key role in energy metabolism, showing its alteration in thyroid and pituitary disorders. It is also called ubiquinone because of its ubiquitous diffusion in organisms and tissues. It is a key component of the mitochondrial oxidative phosphorylation chain as a link between flavoproteins and cytochromes in the inner mitochondrial membrane. It also has many other functions, first of all a powerful antioxidant activity, and new roles in different cellular functions are continuously discovered. This molecule can participate in oxido-reductive reactions in mitochondria, in lysosomes, in the Golgi apparatus and plasma membranes; it also contributes to membrane fluidity.

Dr. Sanjay Agrawal,
Leading Pharmaceutical Consultant and Editor-in Chief of IJMToday, 6/146, Malviya Nagar, Jaipur. Rajasthan.

Moreover CoQ10 can take part in many aspects of the oxido-reductive control of cellular signalling origin and transmission; in fact the auto-oxidation of semi-quinon, formed in various membranes during electron transport, can be a primary source for the H2O2 generation, which activates transcription factors, e.g., NF-κB, to induce gene expression. It is also possible that ROS generation could suppress other genes reinforcing the role of antioxidants in gene regulation. Both hypothyroidism and hyperthyroidism can be associated with OS, moreover thyroid hormone (TH)-induced oxidative damage could be a factor responsible for the progression of heart failure, as suggested by the benefit of T3 administration on antioxidant systems in rat heart after pharmacological-induced hypothyroidism. However, few data exist on the possible diagnostic role of antioxidant measurements; in this review we examine thyroid regulation of antioxidants and OS in cardiac physiology and disease; then we speculate on the situation of low-T3 syndrome (also called "non-thyroidal illness", NTIS, a condition present in chronic disease. This hormonal situation reflects a compensatory mechanism, but the need of replacement therapy is a matter of discussion. Therefore the evaluation of OS parameters could represent a further insight into the pathophysiology of NTIS.

1. Thyroid Hormones and Oxidative Stress Previous studies suggested that the hypermetabolic state of hyperthyroidism is associated with an increase in free radical production, while the hypometabolic state of hypothyroidism symmetrically leads to a reduced free radical production. Indeed both hyperthyroidism and hypothyroidism are associated with enhanced oxidative stress involving enzymatic and non-enzymatic antioxidants. Furthermore, some complications of hyperthyroidism are specifically related to the oxidative stress in target tissues. Thyroid hormones can per se act as oxidants and produce DNA-damage (contrasted by catalase), probably through the phenolic group, similar to that of steroidal estrogens. Many other mechanisms, reviewed by Venditti and Di Meo, can be involved: enhanced nitric oxide (NO)-Synthase (NOS) gene expression with NO overproduction; activation of hepatic NF-κB and the consequent increase of cytokines stimulating ROS generation; uncoupling mechanisms involving UCP-2 and UCP-3, regulated by thyroid hormones; increased turnover of mitochondrial proteins; mitoptosis, regulated by peroxisome proliferator-activated receptor gamma coactivator-1, which is upregulated by T3 administration. Thyroid hormones influence lipid composition of rat tissues and therefore the susceptibility to oxidative stress. However, there is specificity in tissue response, and differential effects of T3 and T4 are possible, as previously reviewed. In rat liver, T3-induced hyperthyroidism was found to be associated with altered lipid-peroxidation indices, including elevated levels of thiobarbituric acid reactive substances (TBARS) and

hydroperoxides. On the contrary, no change in TBARS was observed in homogenized livers from rats made hyperthyroid by administration of T4 over a 4-week period. As regards testis, no significant change was observed in lipid peroxidation (evaluated as TBARS or hydroperoxides) of hyperthyroid adult rats, but hyperthyroidism promoted protein oxidation rate as indicated by an enhanced content of protein-bound carbonyls.[4] In conclusion, it is important to emphasize the fact of a tissue-linked variability in the effects of hyperthyroidism on the activity of antioxidant enzymes (Mn-superoxide dismutase (SOD) or Cu,Zn-SOD, catalase (CAT), glutathione-peroxidase) with differential effects of the two thyroid hormones. The model of cardiac hypertrophy induced by experimental hyperthryroidism in rats has been recently investigated: a T4 treatment in male Wistar rats induced an increase in the left ventricular end-diastolic pressure, coupled with increase of protein oxidation, H2O2, NO metabolites and decrease of GSH/GSSG ratio, vitamin C, total radical trapping antioxidant potential, suggesting the role of oxidative stress in such a model. Vitamin E attenuated these alterations. The involvement of redox activation of AKT1 and JUN/FOS signaling was also demonstrated. The same group also showed that the thyroid-induced cardiac hypertrophy is mediated by angiotensin receptors I and II activation. Also in this case antioxidant administration ameliorated gene and protein expression of angiotensin II receptors and cardiac hypertrophy. Also hyperthyroidism-related hypertension is related to oxidative stress. In male Wistar rats, the administration of tempol, which is a cell membrane-permeable SOD mimetic, reduced blood

pressure acting via antioxidant mechanisms, as demonstrated by a decrease of plasma malondialdehyde (MDA) and urinary excretion of F2 isoprostanes in hypertensive animals, but not in controls. Tempol also increased the slopes of the relationships between renal perfusion pressure and natriuresis. In humans, hyperthyroidism has been associated with reduced circulating levels of alpha-tocopherol and Coenzyme Q10. Coenzyme Q10 showed an increasing trend in hypothyroidism and it appeared to be a sensitive index of thyroid hormones effect, in situations like drug interference, or systemic illness where a low-T3 condition could complicate the interpretation of thyroid hormone levels (see discussion below). Few data are available on CoQ10 levels in human tissues; they seem to be similar to those in plasma: in active proliferating tissue (toxic goiter or neoplasias) CoQ10 concentrations were greater than in unaffected areas. This phenomenon points to an increased CoQ10 synthesis related to the increased metabolic requests; it is in agreement with the increased levels of CoQ9 in liver mitochondria from rats rendered mildly hyperthyroid. However, data on hypothyroidism in humans are conflicting.[5] Baskol et al. showed in a group of 33 patients with primary hypothyroidism elevated MDA and NO levels and low paraoxonase (PON1) activity, while SOD was not different from controls. Interestingly, thyroid treatment decreased MDA and increased PON1, without reaching levels observed in controls. They concluded that a pro-oxidant environment in hypothyroidism could play a role in the pathogenesis of atherosclerosis in these patients. Elevated MDA levels were also observed in subclinical

hypothyroidism; an increased OS was attributed to lack of antioxidants but also to altered lipid metabolism, since MDA showed a correlation with LDL-cholesterol, total cholesterol and triglycerides. Total antioxidant status was similar in overt hypothyroidism, subclinical hypothyroidism and controls. Different studies confirmed the NO elevation in hypothyroid patients. Data on other parameters are conflicting. As PON-1 is concerned, a decreased activity was observed both in hypo and hyperthyroidism, while significant differences were not seen with controls in other studies. Another study showed increased levels of TBARS, but also of antioxidants, such as SOD, CAT and vitamin E. All these parameters correlated with T3; moreover the correlation between T3 and CAT remained significant also when corrected with total cholesterol. While TBARS elevation was also shown in some studies, other studies did not confirm the data in overt hypothyroidism and in subclinical hypothyroidism. We showed low Total Antioxidant Capacity (TAC) levels in hypothyroid patients and increased CoQ10 levels also in secondary hypothyroidism (mainly due to its metabolic role in mitochondrial respiratory chain and therefore underutilized in hypothyroid tissue). In the last case, hypothyroidism has a predominant effect on other conditions that lead to a decrease in CoQ10 levels, such as acromegaly, hypo-adrenalism and hypogonadism. Finally, new perspectives concern DUOX (Dual Oxidase) gene expression, which is crucial for H2O2 generation essential for thyroid peroxidase (TPO)-catalyzed thyroid hormone synthesis. Two oxidases of this family are present in thyroid (DUOX1 and DUOX2) and work

together with maturation factors (DUOXA1 and DUOXA2), which allow DUOX proteins to translocate to the follicular cell membrane and exert their enzymatic activity. Cases of hypothyroidism due to mutation of DUOX or DUOXA genes have been presented in the literature. While defects of this system interfere with thyroid hormone synthesis, another new intracellular ROS generating system has been demonstrated in the human thyroid gland: NADPH oxidase 4 (NOX4); defects in such a system could be associated with thyroid cancer (via activation by the H-Ras oncongene) and Hashimoto's thyroiditis (in such a situation an increased extracellular ROS production causes an augmented ICAM-1 expression and cytokine release). Since hyperlipidemia too can induce oxidative stress, as demonstrated in animals and humans, thyroid hormone effects could be also mediated by interference with lipid metabolism. Lipoprotein plasma levels increase in hypothyroidism, together with a reduction of oxidative metabolism. Hypothyroid patients present higher lipoperoxide (LPx) levels, a significant higher LDL content in the lipid peroxides and higher oxidation rate; they also exhibit elevation in β-carotene levels with higher LDL oxidation. Finally oleic to linoleic acid ratio, which is inversely proportional to oxidative stress, is lower in hypothyroidism.

2. **Thyroid Hormones, Antioxidants and the Heart**
ROS have been indicated as both detrimental and protective, via different pathways, for cardiac myocyte functions, electrophysiology and pharmacology. ROS effects on contractility are well recognized in literature, but recently also cardiac

excitability has been investigated. ROS influence sarcolemmal and mitochondrial ion channels, which are responsible for cardiomyocyte excitability. It is known from the literature that oxidative stress is involved in the clinical course of different cardiopathies and in general it is involved in negative outcomes in cardiovascular disease. ROS have a crucial role in the genesis of atherosclerosis inducing vascular smooth muscle cell (SMC) growth and proliferation, oxidation of LDL, reduction of NO bioavailability, and vascular inflammation, which are characteristic features of the disease. Oxidative stress is also important in myocardial remodeling after a myocardial infarction, inducing fibroblast proliferation and collagen synthesis. Patients with dilatative cardiomyopathies have increased oxidative stress; in particular their erythrocyte membranes show an augmented sensitivity to the lipoperoxides and oxidative damage. The worsening of ventricular dysfunction recognizes as a possible factor myocyte apoptosis related to increased ROS formation. On the other hand, CoQ10 administration has been shown to be useful in the treatment of cardiomyopathies. Therefore a link could be present between TH, antioxidant and cardiac function. In previous works we demonstrated an inverse correlation between plasma Coenzyme Q10 and thyroid hormones, with CoQ10 levels in hyperthyroid patients among the lowest discovered in human diseases. On the contrary, CoQ10 is elevated in hypothyroid subjects, also in subclinical conditions, suggesting the usefulness of this index in assessing metabolic status in thyroid disorders. This correlation is so common that it makes CoQ10 determination a

useful index in clinical situations in which hormone values do not correlate with the metabolic status of the patients. Indeed in Amiodarone treated subjects the drug invariably alters the indexes usually employed to measure thyroid function; in this situation CoQ10 correlates with the metabolic state better than with thyroid hormone levels themselves. The possible explanations for the very low CoQ10 levels in hyperthyroid patients include: decreased synthesis related to competition for tyrosine, which is a common substrate for CoQ or thyroxine synthesis, even if this hypothesis is disconfirmed by experimental data in animals; increased CoQ10 utilization, due to the increased stimulation of energy metabolism; increased degradation; decreased levels of carriers in serum, since it has been demonstrated that the release of VLDL from liver is decreased in hyperthyroid states; similar mechanisms can be invoked to explain high CoQ10 levels in hypothyroid patients.[6] An important index of body antioxidant defense is the antioxidant capacity of blood plasma, which is studied more and more frequently. Representing the functional sum of antioxidants present in plasma, it is a measure of the extracellular antioxidant barrier. In a recent work, TAC was determined during cardiovascular bypass surgery in patients with coronary heart disease: TAC decreased during surgery, but no further decrease in TAC was observed during reperfusion, indicating that it is a relatively stable parameter of the antioxidative barrier of the body

Conclusion

In conclusion thyroid hormones exert a key role in the modulation of antioxidant systems and OS is demonstrated both in hyper-

and hypothyroidism. In the field of hypothyroidism, a debated question is the treatment of NTIS. Even if in the literature data are conflicting, our data suggest considering NTIS as a real hypothyroidism at tissue level and not only as an adaptive response to the conditions mentioned above. In particular, CoQ10 levels seem to be a reliable index of thyroid hormone effects; moreover, OS is a mechanism to be underlined in the physiopathology of NTIS and, again, it can reflect a condition of hypothyroidism. The question of usefulness of replacement therapy is complex and based on standardization of different factors involved: the choice of hormone (T4 or T3); the route of administration (oral or intravenous); and the definition

of clinical endpoints, due to the complexity of clinical models with different interfering factors. When the molecular mechanisms underlying low T3 levels are better understood, it may be possible to choose which patients are likely to benefit from replacement therapy as well as the appropriate schedule of treatment.

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Non-High-Density Lipoprotein Cholesterol:

Of all the lipoproteins, it is the LDL which plays a central role in atherogenesis, right from its initiation in the form of endothelial dysfunction.

There are several other atherogenic lipoproteins in blood and LDL accounts for only about 75% of them. The other significant contributors are cholesterol-enriched remnants of TG-rich lipoproteins such as very low-density lipoprotein (VLDL), intermediate density lipoprotein (IDL) etc. These non-LDL lipoproteins may account for a significant proportion of ASCVD risk, particularly in patients who have elevated TG levels or those in whom LDL-C has already been lowered with statins.

Non-HDL-C is defined as total cholesterol minus HDL-C. Since HDL is the only anti-atherogenic lipoprotein, non-HDL-Ceffectively measures all atherogenic lipoproteins in blood, including LDL, VLDL, IDL, Lp(a), etc.

It is expected to be a more accurate predictor of ASCVD risk as compared to LDL-C.

Non-HDL-C is particularly informative in diabetics who tend to have higher TG levels, and thus have a greater difference between LDL-C and non-HDL-C.

Non-HDL-C seems to predict ASCVD risk equally well regardless of TG levels.

All atherogenic lipoproteins, whether LDL, VLDL or LP(a), contain one molecule of Apo B. Apo B is considered to be the most accurate predictor of ASCVD risk.

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