Thyroid Disorders and their Relevance to Response to Oxidative Challenge

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Abstract

Objective: The extent to which thyroid hormones T4, T3 and thyroid stimulating hormone (TSH) changes can influence lipid peroxidation in plasma as indicated by malondialdehyde MDA levels in response to in vitro challenge with H_2O_2 (5, 10 or 15 mM), as well as, the antioxidant status reduced glutathione (GSH) as the major endogenous antioxidant to be investigated in patient with various thyroid disorders.

Methods: The study included: group (1) twenty hyperthyroid patients and group (2) seventeen hypothyroid patients. Each of these groups was studied by comparing their data with those of twenty-five, sex and age matched healthy control subjects. Hormonal assay was performed using RIA technique. Blood samples were heparinized to obtain plasma to evaluate the susceptibility of plasma to oxidation of lipids to produce malondialdehyde in response to in vitro challenge with 5, 10 or 15 mM H_2O_2. Reduced glutathione content of erythrocytes was measured as indicator for antioxidant state.

Results: Plasma of both hyperthyroid and hypothyroid patients showed greater levels of MDA (130% and 14%, respectively) over the control. Only hyperthyroid patient's plasma expressed a greater susceptibility to in vitro H_2O_2 challenge, as compared to both hypothyroid and control groups. Reduced glutathione contents were lowered in both hyper- and hypothyroid erythrocytes by 40% and 45%, respectively, as compared to controls.

Conclusion: These results indicate that thyroid disorders could precipitate several biochemical changes in tissue that predispose them to oxidative injury. Thus we suggest the use of antioxidants as supplement with the regular therapy of thyroid disorders, in a hope to minimize or delay the chronic complications of thyroid diseases.

Key words: hyperthyroidism, hypothyroidism, MDA, GSH.

Introduction:

Thyroid hormones , among other hormones, play a vital role in the fetal development as well as throughout the life by affecting most of the metabolic process in almost all tissues by regulating gene expression , tissue differentiation and general development. [1]

Among their immediate effects, thyroid hormones may influence the physical state of membranes and consequent changes in membrane composition. This may be due to their effects on metabolism which is reflected primarily to membrane acyl changes [2, 3]. Such lipid modifications could protect biomembranes against increased oxidative attacks to tissue, cardiolipin – the main mitochondrial lipid that most profoundly altered fraction by thyroid hormones changes – as a result of modified mitochonderial activities. [4]

Recently, the concept about the possible presence of a relation between thyroid function disorders and free oxygen radicals has greater importance [5, 6]. As some investigators have reported that some animal studies showed that the rate of lipoxidation increases in both hyper- and hypothyroid states via the same events based on different mechanisms [1]. Both processes exhibit a differential time course of changes that may represent differences in the susceptibility of target molecules to free radical attack and/or in the efficiency of defense mechanisms. [7, 8]

This study was designed to elucidate the link between thyroid hormone levels and lipid peroxidation in human plasma and the protective antioxidant system in response to in vitro oxidative challenge with hydrogen peroxide.

Subjects & Methods

We have total plasma T_4 , T_3 and TSH levels determined by Radioimmunoassay [9,10,11] using Immunotech Kits-Gzech for sixty-two subjects ; twenty of them pre-diagnosed as hyperthyroid, seventeen of them as hypothyroid by a senior physician , based on their hormone analysis (Table –1-) and clinical assessment .

heparinized blood samples were used to obtain plasma to measure lipid peroxidation end product malondialdehyde (MDA) by Gilbert et al method [12] , before and after subjecting each sample to in vitro oxidative challenge with H_2O_2 by incubating aliquots of each sample with (0 mM, 5 mM, 10 mM and 15 mM) for 30 minutes at 37 ^oC.

The antioxidant status was assessed using washed erythrocytes obtained from the heparinized blood samples in order to measure reduced glutathione content (GSH) by Godin et al method. [13]

Statistical analysis:

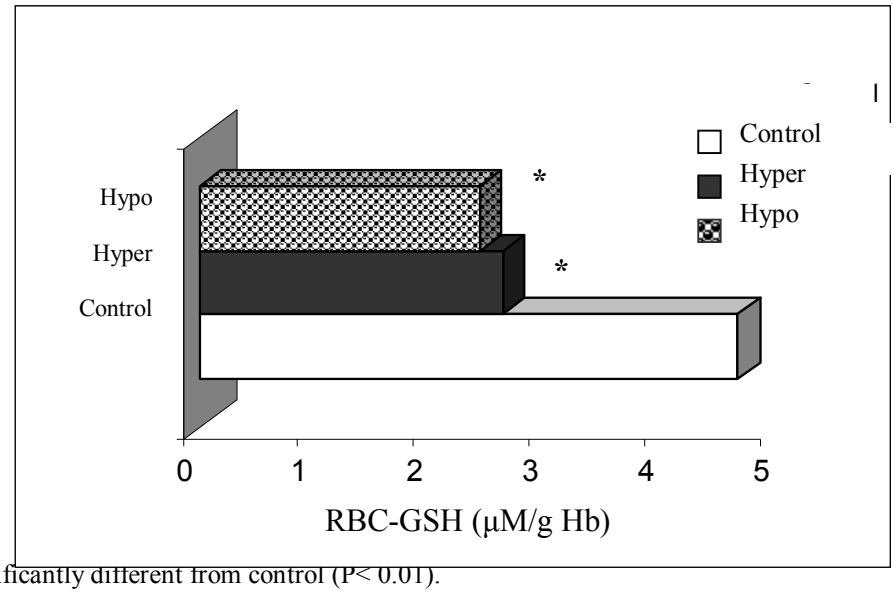
All the estimates were expressed as mean ± SD. The results were compared using analysis of variance (ANOVA). Differences of $P< 0.05$ were considered significant.

Results:

Plasma samples from hyperthyroid and hypothyroid patients showed 130% and 14%,

respectively, increment in basal MDA concentration. However, lipid peroxidation index (MDA) level in hypothyroid patients revealed no significant change over the control values (table–1).

Erythrocyte suspension from hyperthyroid and hypothyroid patients were analyzed for their content of GSH results reflected a significant reduction as compared to the controls by 40%, 45%, respectively , as shown in figure –1.



* Significantly different from control (P< 0.01).

Figure –1-Glutathione content of erythrocytes in the studied groups

Table –1-Plasma MDA concentration (µM/L) in response to in vitro challenge with H_2O_2

Group	**H_2O_2 concentration (mM)**			
	0	5	10	15
Control	0.42 ± 0.12	0.81 ± 0.28	1.07 ± 0.17	1.44 ± 0.29
Hyperthyroid	0.97 ± 0.29*	1.26 ± 0.21*	1.64 ± 0.25*	2.29 ± 0.48*
Hypothyroid	0.48 ± 0.21	0.87 ± 0.17	1.19 ± 0.23	1.29 ± 0.36

* Significantly different from control within the same H_2O_2 concentration (P< 0.01).

Discussion

According to our point of view, oxygen free radical production and thus lipid peroxidation could be modified by thyroid disorders, since the general metabolic function of thyroid hormones is to increase oxygen consumption in all tissues, and to control the basal metabolic rate. [1]

Our results reflect an increased rate of lipid peroxidation in the hyperthyroid group which could be attributed to the enhanced pro- oxidant production, [14, and 15] presented as oxidative stress at cellular level in tissues which are subjected to the action of thyroid hormones [16]. This explanation supported by the augmented response to in vitro challenge with hydrogen peroxidation by the hyperthyroid group over that recorded for the hypothyroid and control groups (table-2).

Furthermore, cellular redox is controlled by thioredoxin and glutathione systems that scavenge harmful intracellular reactive oxygen species [17]. As presented in Figure-1, glutathione level is reduced significantly in both hyper- and hypothyroid patients groups via different mechanisms. Some reports had mentioned that hepatic glutathione stores are depleted in hyperthyroid rats [16, 18]. The allergenic response in the hyperthyroid state is accompanied by decreased antioxidant cellular activity as a result of increased rate glutathione consumption [19]. Whereas, hypothyroidism increased glutathione status presumably by reducing radical production which would otherwise consume this important scavenger [20], additional factor in hypothyroid state could be related to the lowered level of T_3 which have an important role in the expression of enzyme activities for glutathione such as glutathione peroxides [21] and alphaglutathione S- transferase [22].

From the above, we can say that both sides the equation that is involved in the maintenance of the redox state of the cell (i.e. the pro- oxidants and the antioxidants) are modified by thyroid functional disorders. Therefore, to evaluate the relative influence of each of the studied parameters on the redox state in cells for each condition, we calculated the ***antioxidant /pro-oxidant ratio***, represented by ***GSH /MDA*** ratio, as shown in table 3. The ratio was significantly reduced in both hyper- and hypothyroid patients as compared to the controls (2.71, 4.96 and 11.12, respectively), indicating a greater disturbances in the hyperthyroid patients, which was reflected by the greater increment in MDA production in response to a given concentration of H_2O_2 when compared to hypothyroid or control samples (Table- 2). Such increased in vitro susceptibility may be extrapolated to the in vivo situation of thyroid disorders. [23]

Seven et.al. Had reported that such modification in the ratio could be improved after supplementation with vitamin C, besides antithyroid treatment of a group of hyperthyroid patients [24]. As the major complications of hyperthyroidism are presented as myopathies and cardiomyopathy which may be related to the disturbances in the mitochondrial function and glutathione- dependent antioxidant system that are important for the maintenance of the structural and functional integrity of the muscular tissue [25].

In conclusion the increase in plasma thyroid hormones might be related to the oxidative damage in the body; therefore, we suggest the use of antioxidant drugs to strength the antioxidant defense system, in addition to the conventional antithyroid treatment, in a hope to minimize the thyroid patient's serious complications.

Table –3-GSH / MDA * Ratio in the studied groups

Control **N=25**	**Hyperthyroid** **N= 20**	**Hypothyroid** **N = 17**
11.12 ± 2.01	2.71 ± 0.53	4.96 ± 0.78

* MDA in this table represents the basal values in all groups

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