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ORIGINAL ARTICLE

Oxidative Stress in Hypo and Hyperthyroidism

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Abstract: Thyroid hormones from the thyroid gland are necessary for the normal development of body organs. It was demonstrated that NO participates in the regulation of thyroid function. NO brings about oxidation reactions which will produce free radicals, and can start chain reactions that damage cells. This leads to the production of ROS. These oxidants can damage cells by starting chemical chain reactions such as lipid peroxidation, or the oxidizing DNA or proteins. The oxidation status was assessed by measuring the level of nitric oxide, total antioxidants and the antioxidant enzyme, Super Oxide Dismutase (SOD) in the blood. All the data were analyzed by one-way ANOVA followed by paired t-test. The level of significance was considered at P> 0.05.Serum nitric oxide and total antioxidants were decreased significantly in hyperthyroidism and almost no change in hypothyroidism when compared to the normal levels. Further, erythrocyte super oxide dismutase (SOD) was significantly high in patients with hyperthyroidism and it is almost same in hypothyroidism and normal controls. The result indicates that the thyroid hormone has a pro-oxidant effect and increases the oxygen free radical production and hence the resultant decrease in antioxidant state in case of hyperthyroidism when compared to the normal and hypothyroidism.

Key words: Hypothyroidism, Hyperthyroidism, Nitric oxide, Super oxide dismutase

Introduction

Thyroid hormones from the thyroid gland are necessary for the normal development of body organs. When the thyroid becomes overactive and releases too much T_3 and T_4 into the blood, leading to thyrotoxicosis. Hypothyroidism is the opposite condition. Primary hypothyroidism happens when the thyroid itself fails. In secondary hypothyroidism the "hypothalamic-pituitary-thyroid-axis" works inadequately. Hypothyroidism can also be caused by a lack of iodine in the diet, which prevents the thyroid from making enough hormones, or as a side effect of certain drugs, like lithium. On a worldwide basis iodine deficiency is the commonest cause of hypothyroidism. The previous studies showed that a significant changes in T_3, T_4 and TSH level during different thyroid state with different stressors, indicating the relationship between the level of thyroxin and oxidative stress [1]. Recent studies suggests that NO participates in the regulation of thyroid function. Hence it is possible that NO is one of the factors that plays a role in the regulation of thyroid vascularity and blood flow. These oxidation reactions can produce free radicals, which start chain reactions that damage cells. Antioxidants terminate these chain

reactions by removing free radical intermediates, and inhibit other oxidation reactions by being oxidized themselves. This leads to the production of reactive oxygen species which includes hydrogen peroxide (H_2O_2), hypochlorous acid (HClO), and free radicals which as the hydroxyl radical (-OH) and the superoxide anion (O_2^-). The hydroxyl radical is particularly unstable and will react rapidly and non-specifically with most biological molecules. These oxidants can damage cells by starting chemical chain reactions such as lipid peroxidation, or by oxidizing DNA or proteins. Super (SOD) is another important antioxidant defense in nearly all cells exposed to oxygen. Super oxide Dismutase repairs cells and reduces the damage done to them by super oxide .Studies have shown that SOD acts as both an antioxidant and anti-inflammatory in the body, neutralizing the free radicals that can lead to wrinkles and precancerous cell changes. Though many studies have explained the several biochemical parameters in thyroidism, the oxidative state in thyroidism was not well documented. Therefore the present study was undertaken to determine whether hyperthyroidism and hypothyroidism have any effect on the oxidative state of the body.

Materials and Methods

The present study was undertaken to investigate whether hyperthyroidism and hypothyroidism has any effect on the oxidative state of the body. The oxidation status was assessed by measuring the level of nitric oxide, total antioxidants and the antioxidant enzyme, Super Oxide Dismutase (SOD) in the blood. The study has involved 80 patients; of which 40 were suffering from hyperthyroidism (Group-2) and remaining 40 were suffering from hypothyroidism (Group-3). It also included 40 age and sex matched healthy peoples as controls (Group-1). Both in-patients and out-patients who attended for treatment at K.S. Hegde Charitable hospital, Mangalore, were included after an informed consent from the concerned subjects. The patients who had a long history of smoking and the patients who were suffering from other diseases along with thyroidism were excluded from the study. The blood was collected from median cubital vein by venipuncture. After aseptic precautions, 5ml blood was drawn from the site. After sampling, the serum samples were stored at -4ºC until analysis. The serum T-3, T-4; TSH levels were estimated by ELISA method to group them as normal subjects, hypothyroid and hyperthyroid patients. The total antioxidant capacity was estimated using Phosphomolybdenum method. The Super oxide Dismutase activity was estimated by Nitro blue tetrazolium (NBT) method. The Nitric oxide level was estimated by Griess reagent method.

Statistical analysis: The values were expressed as mean ± SD. All the data were analyzed by one-way ANOVA followed by paired t-test. The level of significance was considered at $P > 0.05$.

Results

The aim of the present study was to analyze the oxidation state in hypo and hyperthyroidism. The oxidation state was assessed by measuring nitric oxide, total antioxidants and activity of superoxide dismutase enzymes in the blood serum of 40

hyper and 40 hypothyroidism patients. Serum nitric oxide and total antioxidants were decreased significantly in hyperthyroidism and almost no change in hypothyroidism when compared to the normal levels. Further, erythrocyte superoxide dismutase (SOD) was significantly high in patients with hyperthyroidism and it is almost same in hypothyroidism and normal controls (Table-1, Fig-1). The result indicates that the thyroid hormone has a pro-oxidant effect and increases the oxygen free radical production and hence the resultant decrease in antioxidant state in case of hyperthyroidism when compared to the normal and hypothyroidism.

Table 1: The clinical characteristics of normal subjects and patients with hyper and hypothyroidism. The values are expressed as Mean **±** S.D, N=40 in each group.

Parameters	**Group-1**	**Group-2**	**Group-3**
Nitric Oxide (µg/ml)	469.16 ± 42.58	139.59 ± 13.96*	360.41 ± 25.69
SOD (units/mg protein)	3.93 ± 0.39	5.58 ± 0.52*	3.83 ± 0.26
Total Antioxidant (µg of α-tocopherol/ml)	189.64 ± 10.85	43.61 ± 6.88*	191.16 ± 21.95

Note: Group 1, Group 2 and Group 3 includes normal (control) subjects, Hyperthyroid and Hypothyroid patients respectively.*P > 0.0001 in Group-2 with respect to nitric oxide, SOD and Total antioxidant level, whereas no significant change between Group 1 and Group 3.

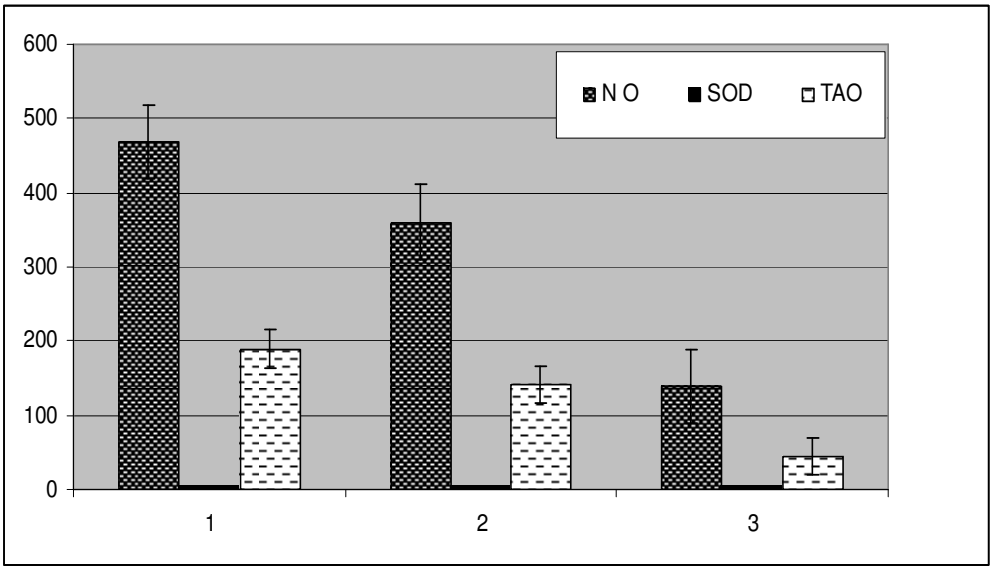

Fig 1: Concentration of Nitric oxide (NO), Super oxide desmutase (SOD) and Total antioxidant (TAO) in Group 1 (Control), Group 2 (Hyperthyroid) and Group 3 (Hypothyroid) patients respectively .

Discussion

Thyroid hormones are necessary for the normal development of body organs. When the thyroid becomes overactive and releases too much T_3 and T_4 into the blood, leading to thyrotoxicosis. In primary hypothyroidism happen when the thyroid itself fails. In secondary hypothyroidism the "hypothalamic-pituitary-thyroid-axis" works inadequately. Hypothyroidism can also be caused by a lack of iodine in the diet, which prevents the thyroid from making enough hormones, or as a side effect of certain drugs, like lithium. The earlier Studies showed that there is a significant changes in T_3, T_4 and TSH level during different thyroid state with all the employed stressors, indicating some relationship between the level of thyroxin and oxidative stress. This indicates that thyroid hormones play a vital role in the generation of universal oxidative stress [1]. It was also suggested that the hyper metabolic state in hyperthyroidism is associated with increase in free radical production and lipid peroxide levels [2]. Whereas, the hypo metabolic state induced by the hypothyroidism is associated with a decrease in free radical production [3]. Another study reported that oxidative stress plays an important role in hyperthyroidism-induced tissue damage, as well as in the development of autoimmune disorders. Hyperthyroidism caused an increase in SOD and CAT activities [4].

It was demonstrated that in induced hypothyroidism the lipid peroxidation was not altered whereas in hyperthyroid rats' lipid peroxidation increased in liver and heart but not in skeletal muscle. This indicates that the susceptibility to oxidative challenge was increased in all tissues of hyperthyroid rats and in heart and muscle of hypothyroid animals [5]. Nitric oxide mediates a wide array of cellular functions in many tissues. It is generated by three known isoforms of nitric oxide synthases (NOS). The effects of thyroid status on nitric oxide synthases (NOS) gene expression in the rat hypothalamic Para ventricular (PVN) and supraoptic nuclei (SON) in Propylthiouracil (PTU)-induced hypothyroidism in male rats produced a highly significant reduction in NOS gene transcription in the PVN and SON, as assessed by quantitative in situ hybridization histochemistry with a specific oligodeoxynucleotide probe.

The addition of T_3 (40 micrograms/kg) to the PTU-containing diet completely prevented reduction in NOS transcripts. Hyperthyroidism, induced by adding 160 micrograms/kg T_3 to the food, more than doubled the prevalence of NOS transcripts in the PVN and SON after a similar time. Up-regulation of NOS gene transcripts induced by the osmotic stimulus of chronic salt loading was markedly attenuated by PTU-induced hypothyroidism [6].

Hyperthyroidism is a hyper metabolic state accompanied by increased oxygen utilization, increased production of reactive oxygen species and consequently measurable changes in anti oxidative factors. This impaired anti-oxidative factor leads to the development and presence of oxidative stress in patients with hyperthyroidism [7]. Hyperthyroidism resulted in a marked increase in intracellular antioxidant enzymes, i.e., super oxide dismutase, catalase and glutathione peroxidase activities as compared to the controls. Extra cellular anti-free radical scavenging

systems potential, measured by glutathione reductase activity and total antioxidant status level, was found to be significantly decreased in untreated Graves' patients. Treatment with thiamazole resulted in normalization of the free radical and antioxidant activity indices. The obtained results indicates that an enhanced generation of reactive oxygen species and impairment of cellular and extra cellular antioxidant systems potential in patients with Graves' disease. The attainment of euthyroid state led to an improvement in oxidative stress indices and antioxidant potential parameters [8].

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