Original Research Article

Role of oxidative stress in thyrotoxicosis

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Abstract

Thyrotoxicosis is a clinical syndrome that results when excessive levels of active thyroid hormones T_3 and T_4 are secreted into the circulation. In thyrotoxicosis oxidative stress is implicated in the causation of clinical features like myopathy, myocardial insufficiency and ophthalmopathy. Oxidative change in thyrotoxicosis was assessed by measuring level of lipid peroxidation product malondialdehyde (MDA) and activity of antioxidant enzyme superoxide dismutase (SOD) in the blood of 18 thyrotoxic patients and 22 healthy euthyroid controls. Serum MDA level was significantly increased and serum SOD activity was very significantly decreased in the cases when compared to controls. **Conclusion:** The present study confirms the presence of oxidative stress in thyrotoxicosis. This warrants nutritional support with antioxidant agents in thyrotoxicosis.

Key Words: oxidative stress, thyrotoxicosis

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Received Date: 20/08/2017 Revised Date: 16/09/2017 Accepted Date: 01/10/2017

Access this article online

Quick Response Code:

Website: www.statperson.com

Volume 7
Issue 4

INTRODUCTION

Thyrotoxiosis is one of the most common afflictions involving the endocrine system. It is a clinical syndrome that results when excessive levels of active thyroid hormones T_3 and T_4 are secreted into the circulation[1]. Both of these hormones have profound effect of increasing the metabolic rate in the body. Most of the clinical features of thyrotoxicosis is related directly to the increased metabolic activity caused by excess levels of thyroid hormones in the circulation[1]. Clinical features include heat intolerance, weight loss, warm moist skin, anxiety, diarrhoea, tremor, cardiovascular manifestations like tachycardia and atrial fibrillation, proximal myopathy and ophthalmopathy[2]. Most of these manifestations usually abate when a normal metabolic state is restored[3] by the use of antithyroid drugs. But the clinical features like myocardial insufficiency and ophthalmopathy are not fully amenable to antithyroid drugs. Their etiopathogenesis is also not well understood[4,5,6].

Oxidative stress in the pathogenesis of thyrotoxicosis: In hyperthyroidism excessive level of thyroid hormones are secreted to the circulation with a loss of normal feedback mechanism controlling the secretion of thyroid hormone. Thyroid hormones increase the metabolic activity of almost all tissues in the body. The basal metabolic rate can increase to 60-100% above normal when large quantities of hormones are secreted. The rate of utilization of food for energy is greatly accelerated. Increased metabolism due to hyperthyroidism leads to dysfunction of the mitochondrial respiratory chain, resulting in the generation of more reactive oxygen species like superoxide anion, hydrogen peroxide and hydroxyl radical[11]. These potentially toxic free radicals cause increased lipid peroxidation damage to cellular membranes, mitochondrial damage, inhibit nucleic acid and inactivate cellular enzymes[12]. This may be the cause of systemic manifestations like myopathy and myocardial insufficiency in thyrotoxicosis[7]. Invitro studies suggest a pathway through which oxygen free radicals may contribute to the retro-ocular fibroblast proliferation observed in patients with Grave's ophthalmopathy[8]. There is no satisfactory treatment modality to alleviate these features seen in thyrotoxicosis. Existing therapies for both thyrotoxic and the ophthalmopathic

How to cite this article: Geetha P A, Ajaykumar B, Parvathi K, Sreejayan M P. Role of oxidative stress in thyrotoxicosis. *International Journal of Recent Trends in Science and Technology* October to December 2017; 7(4): 12-15 http://www.statperson.com

manifestations are palliative in that they may relieve but do not cure the disease. At this state it is desirable to look to the oxidative state in thyrotoxicosis. In this study the oxidative status in thyrotoxicosis was assessed by comparing the levels of lipid peroxidation product malondialdehyde (MDA) and the activity of the antioxidant enzyme superoxide dismutase (SOD) between normal healthy euthyroid individuals and hyperthyroid patients.

MATERIALS AND METHODS

The patients for the present study were from the outpatients attending surgical OP of Govt. Medical College, Kozhikode. The present study was conducted on two groups consisting of 18 hyperthyroid patients and 22 age and sex matched healthy euthyroid controls

Exclusion Criteria

Smokers and patients clinically proven to have diabetes, coronary artery disease, renal diseases and hypertension which can alter MDA levels were excluded from the study. Thyroid function tests of each subject of both groups were done. Malondialdehyde was measured in serum by the method based on Valipasha and Sadasivadu's procedure for estimation of malondialdehyde[13] The serum SOD activity was measured by the method suggested by Marklund and Marklund 1974 (Modified by Nandi *et al* 1988)[14.] Analysis was done in UV-Vis spectrophotometer 118 (Systronics).

Statistical Analysis

- Baseline parameters were compared using **Fischers exact test**, **Chi squared test** and **unpaired t test** (two tailed and assuming different SD).
- Comparison of evidence of oxidative stress between patients and control was performed using **unpaired t test** (one tailed and assuming different SD).
- **Correlation test** was performed using Spearman's correlation test (Non-parametric correlation test) to determine variation of evidence of oxidative stress with changing values of evidence of hyperthyroidism.

P value of <0.05 was considered significant. Values are expressed as numbers, percentage and mean ± standard deviation.

RESULTS

Base line factors were compared between control and thyrotoxic patients – shown in table 1.

Table 1: Comparison of baseline factors

	Control (22)	Patients (18)	P value
Age	35.5 ± 10.55	36.11 ± 9.3	0.85
% male	8 (36.36%)	9 (50%)	0.58
Non-vegetarian	20 (90.91%)	15 (83.33%)	0.64
T_3 (ng/ml)	1.31 ± 0.28	3.19 ± 1.31	<0.01
T_4 (μg/dl)	9.86 ± 1.68	17.6 ± 4.45	<0.01
TSH (μIU/ml)	2.06 ± 1.36	0.13 ± 0.38	<0.01

Values expressed as mean ± S.D and percentage Age, sex and non vegetarian status were comparable between the cases and controls. T_3, T_4 and TSH values showed significant difference between the cases and controls. Baseline characteristics of included thyrotoxic patients are shown in table 2.

Table 2: Baseline characteristics of included thyrotoxic patients

Total no. of patients	18 (100%)
% patients on antithyroid drugs	6 (33.33%)
% having exophthalmos	5 (27.78%)
% showing CVS manifestations	5 (27.78%)
% showing muscle weakness	5 (27.78%)

Comparison of evidence of oxidative stress between control and thyrotoxic patients are shown in table 3.

Table 3: Comparison of evidence of oxidative stress

	Control	Patients	P value
MDA (nmol/100ml)	50.87 ± 9.7	59.68 ± 16.02	0.03*
SOD (units/ml)	17.81 ± 0.89	17.01 ± 1.23	0.01**

Values expressed as mean ± standard deviation, *Significant, ** Very significant

Evidence of oxidative stress with degree of hyperthyroidism was compared shown in table 4

Table 4: Comparison of evidence of oxidative stress with degree of hyperthyroidism (correlation value and P value)

	T_3	T_4
MDA – r (Pvalue)	-0.21 (0.39)	-0.42 (0.08)
SOD – r (Pvalue)	0.09 (0.73)	0.16 (0.54)

There is no significant correlation between MDA and, SOD with degree of hyperthyroidism.

DISCUSSION

Free radical mediated injury is suggested in the pathogenesis of myocardial insufficiency, myopathy and ophthalmopathy in thyrotoxicosis[7,8,9]. The present study was conducted to assess the oxidative state in thyrotoxicosis by comparing the levels of lipid peroxidation product – malondialdehyde and the activity of antioxidant enzyme – superoxide dismutase between normal healthy euthyroid individuals and hyperthyroid patients. Baseline parameters were compared in both

study groups. Age, sex and non-vegetarian status can affect the oxidative status of individuals. As age advances the metabolic rate of the body decreases[17]. Metabolic rate has got influence on the oxidant stress of the individual. As metabolic rate increase, there is elevation in the oxidant stress of the individual. Male sex hormones increase the metabolic rate by about 10-15% and this can also affect the study[17]. In vegetarians due to the relatively increased intake of fruits and vegetables which are rich in antioxidants, the oxidative stress will be less in vegetarian when compared to non-vegetarians. In the present study, mean age, sex and non-vegetarian status ratio were comparable in both study groups. There was significant difference in T_3, T_4 and TSH values between the study groups. Serum MDA levels were significantly increased in hyperthyroid patients compared to euthyroid controls. Similar result was shown by the study conducted by Vikram Kesar *et al*[7]. Studies conducted by Bianchi G *et al*[9], Komosiaska-Vassev *et al*[10], Seven R *et al*[18] and Guerra LN *et al*[19]on serum of patients with Graves' disease also showed similar results. Increased metabolism due to the elevated levels of T_3 and T_4 in hyperthyroid individuals leads to the dysfunction of the mitochondrial respiratory chain, resulting in elevated formation of the reactive oxygen species like superoxide radical, hydroxyl radical which will cause increased lipid peroxidation damage to membranes of cells and sub cellular organelles which is evidenced by the elevation in MDA level. Serum superoxide dismutase activity was significantly decreased in thyrotoxic patients compared to controls. Similar study conducted by Vikram Kesar *et al*[7] showed increased activity of intracellular SOD. Studies conducted on Graves' disease by Guerra LN *et al*[19], Seven R *et al*[18], Komosinska-Vassev K *et al*[10] and Hara H *et al*[20] showed increased activity of SOD compared to controls. Study conducted by Wilson R *et al* on Graves' disease showed decreased activity of SOD. Free radicals cause increased lipid peroxidation damage of cellular and sub cellular membranes, inhibits nucleic acids and protein synthesis and inactivate cellular enzymes[16]. The excessive generation of free radicals in thyrotoxicosis may be inactivating the enzyme systems in the body. This may be the cause of decreased SOD activity observed in the present study. Thyroid hormones induce or repress proteins by increasing or decreasing gene transcription. Very high concentrations of T_3 inhibit protein synthesis[15]. The decreased SOD activity observed in thyrotoxicosis can be due to the repressing effect of T_3 on SOD synthesis. To establish this further elaborate study is needed. No significant correlation was observed in the levels of MDA, and SOD with varying values of T_3 and T_4 in hyperthyroid patients. Hence T_3 and T_4 values cannot be taken as predictors of degree of oxidant stress in hyperthyroid patients.

CONCLUSION

In the present study, the following results were obtained in thyrotoxicosis

a) The level of lipid peroxidation product – Malondialdehyde is elevated.

b) There is deficiency in the activity of antioxidant enzyme – superoxide dismutase in serum.

c) There is no definite correlation between MDA, SOD activity with varying values of T_3 and T_4 in thyrotoxicosis.

The above data confirm the presence of oxidant stress in thyrotoxicosis. This warrants nutritional support with antioxidant agents which are defective in thyrotoxicosis. T_3 and T_4 values cannot be taken as predictors of degree of oxidant stress in hyperthyroid patients.

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Source of Support: None Declared
Conflict of Interest: None Declared