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COMPARATIVE STUDY ON COMBINED EFFECT OF TREADMILL EXERCISE TEST AND HYPOTHYROIDISM ON OXIDATIVE STRESS OF SUB-CLINICAL AND OVERT HYPOTHYROIDISM PATIENTS

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ABSTRACT

Background: The present study was conducted on patients suffering from subclinical and over hypothyroidism and healthy controls. **Materials and methods:** The sample size was calculated to be 100 (50 cases and 50 healthy controls). They were recruited from the outpatient department with history of overt or subclinical hypothyroidism with no clinical evidence of CAD. Thyroid related parameters (FT4 and TSH) and cardiac parameters (SBP, DBP, PR, ECG HR, QRS) and oxidative stress biomarker (pre-TET MDA and post-TET MDA) were measures and correlated. **Results:** The mean FT4 was 0.80±0.23 in the case group and 0.75±0.30 in the control group. The TSH was 13.32±9.71 in the case group and 3.19±4.26 in the control group. The pre-TET MDA was 18.74±6.56 in the case group and 3.30±0.72 in the control group. The post-TET MDA was 20.62±6.56 in the case group and 5.45±0.89 in the control group. Statistically significant difference exists between the groups (p value≤0.05). **Conclusion:** The present study shows that there is a positive correlation between FT4 and post- TET MDA and a positive correlation between TSH and post-TET MDA. That means, oxidative stress as well as MDA levels will increase if there is any increase in the FT4 level and TSH level.

KEYWORDS: Sub-clinical hypothyroidism, overt hypothyroidism, treadmill exercise test, FT4, TSH.

INTRODUCTION

Hypothyroidism is a complex disease with multiple physiological and psychological signs and symptoms that can have a considerably negative impact on quality of life including exercise-related constraints and reduced physical performance. Hypothyroidism can be classified on the basis of its time of onset (congenital or acquired hypothyroidism), its causal dysfunction at the thyroid gland or hypothalamic-pituitary level (primary or central hypothyroidism), and its severity. Oxidative Stress is defined as the unbalancing between production of free radicals, molecules characterized by high reactivity due to one or more unpaired electrons in the external orbital and antioxidant defences in the biological systems. Presently it is considered an important pathogenic mechanism in different diseases. Free radicals may cause lipid peroxidation & damage to macromolecules & cellular structures of the organism, endothelium and erythrocytes. There are several biochemical markers showing the extent of ongoing oxidative stress in the body. Thyroid hormones have well- known effects on mitochondrial oxygen consumption but data regarding the role of hypothyroidism on oxidative stress is not adequate.[1-3] Oxidative stress results in imbalance between the antioxidant defence systems and the rate of production of reactive oxygen species (ROS). It not only leads to lipid peroxidation and oxidative DNA damage but also interferes with physiologic adaptation and intracellular signal transduction. The resulting change in the intracellular redox status leads to the activation of protein kinases like Tyrosine kinase, Protein kinase C, and the Mitogen-activated protein kinase cascade leading to altered cellular functions.[4, 5]

Excess thyroid-stimulating hormone (TSH) per se might alter oxidative stress processes. Hypothyroidism-induced dysfunction of the mitochondrial respiratory chain can lead to the accelerated production of free radicals. Regular physical activity (exercise training) is an important factor in the prevention and treatment of cardiovascular disease. Exercise training improves vascular endothelial function with improved nitric oxide bioavailability as a result of enhanced synthesis and reduced oxidative stress-mediated destruction. However, acute-intense exercise does not elicit the same response as long- term exercise training. Although regular exercise training decreases oxidative stress, strenuous acute physical exercise can cause oxidative stress and subsequent damage to cellular proteins, lipids and

nucleic acids as well as changes to the glutathione system.[6-9]

The treadmill exercise test (TET) is a short-term exercise testing and is widely used in subjects with suspected coronary artery disease. TET is one of the most frequently used non- invasive tests to assess the patients with suspected or proven coronary artery disease. Few previous studies have reported that TET increases oxidants, decreases Total Antioxidant capacity and Vitamin C namely, the balance shift towards oxidative side, but this stress is not enough to produce DNA damage. However, the available data concerning Oxidant stress and Antioxidant on the combined effect of both Sub-clinical and Overt Hypothyroidism and Acute Exercise Test are scanty and inconclusive.[10]

Therefore, the study was conducted to determine whether Treadmill Exercise Test (TET) is causing any additional effect on the Oxidative Stress Parameters of Sub-clinical and Overt Hypothyroidism cases.

MATERIALS AND METHODS

The study was conducted in the Department of Physiology and Biochemistry of Calcutta National Medical College, Kolkata. The ethical approval was obtained from the institutional ethical committee. The sample size was calculated to be 100 (50 cases and 50 healthy controls). They were recruited from the outpatient department with history of overt or subclinical hypothyroidism with no clinical evidence of CAD.

Inclusion criteria: Adult patients (age>18 years) with newly diagnosed (treatment-naïve) Subclinical (SCH) and Overt hypothyroidism (OH) was included in the study.

Exclusion criteria: Subjects with Hypertension, Cardiovascular disease, Diabetes Mellitus, Dyslipidaemia, Acute or Chronic Inflammatory disease, Immunological disease, History or Presence of Neoplastic Disease, Alcohol consumption greater than 40 ml per day, or Medication use, including Mineral or Vitamin supplements, Smoking and Body Mass Index >30 kg/m2 was excluded. In addition, the individuals with Angina or any other Cardiac or Pulmonary symptoms potentially limiting exercise performance and not reaching target heart rate (THR) was excluded as well.

Methodology: Descriptive data of participants like name, age, sex, personal history, occupation, were obtained by interviewing the patients. Each of the patient's proper history was recorded on predesigned and pretested proforma. They underwent thorough physical examination. All of them had normal 12 lead ECG. All patients were subjected to the following investigations at the time of inclusion into the study: Routine Hemogram, Glycosylated Haemoglobin, FBS & PPBS, Lipid Profile (Total Cholesterol, Triglycerides), Blood Urea and Serum Creatinine, Urine Routine and Microscopic examination, X-ray chest (PA view)., Resting Electrocardiogram. The main study variables were Serum FT4 & TSH and Pre and Post TET Serum Malondialdehyde (MDA) Level.

Statistical analysis: The data was tabulated in Microsoft Excel software and analyzed with SPSS V.24 software. Independent t test, one way ANOVA and Pearson's chi square test were used for the comparisons between the groups and Pearson's correlation coefficient was used for assessing the correlation between the variables. The p value≤0.05 was considered as statistically significant.

RESULTS

The results of the study showed that, the mean age was 30.38±4.61 years in the case group and 25.44±4.89 years in the control group. Statistically significant difference exists in the mean age between the groups (p value≤0.05); the case group had 26% male and 74 % female and the control group had 48% male and 52% female. Statistically significant difference exists in the gender distribution between the groups (p value≤0.05); the case group had 64% housewives, 4% drivers, 12% labourers and 20% students and the control group had 22% housewives, 8% drivers, 10% labourers and 60% students. Statistically significant difference exists in the distribution of occupation between the groups (p value≤0.05); the case group had 80% patients from low socioeconomic status and 20% patients from middle socioeconomic status and the control group had 98% patients from low socioeconomic status and 2% patients from middle socioeconomic status. Statistically significant difference exists in the distribution of socioeconomic status between the groups (p value≤0.05) (Table 1).

The highest proportion of the patients in the case group was taking Eltr 50 (30%) and lowest proportion of the patients in the case group was taking Eltr 150 (8%) or Eltr 100 (8%). The highest proportion of the patients in the case group was having the disease for 2 years (28%) and lowest proportion of the patients in the case group was having the disease for 8 years (1%).

Table 1: Demographic details.

Variables		Case	Control	p value
Age (years)		30.38±4.61	25.44±4.89	<0.001
Sex	Male	13 (26.0%)	24 (48.0%)	0.022
	Female	37 (74.0%)	26 (52.0%)	
Occupation	Housewife	32 (64.0%)	11 (22.0%)	<0.001
	Driver	2 (4.0%)	4 (8.0%)	
	Labourer	6 (12.0%)	5 (10.0%)	
	Student	10 (20.0%)	30 (60.0%)	
Socioeconomic status	Low	40 (80.0%)	49 (98.0%)	0.004
	Middle	10 (20.0%)	1 (2.0%)	

The Comparison of the study variables showed that, the mean FT4 was 0.80±0.23 in the case group and 0.75±0.30 in the control group; the TSH was 13.32±9.71 in the case group and 3.19±4.26 in the control group. Statistically significant difference exists in the TSH between the groups (p value≤0.05); the pre-TET MDA was 18.74±6.56 in the case group and 3.30±0.72 in the control group. Statistically significant difference exists in the pre-TET MDA between the groups (p value≤0.05); the post-TET MDA was 20.62±6.56 in the case group and 5.45±0.89 in the control group. Statistically significant difference exists in the post-TET MDA between the groups (p value≤0.05); the SBP was 121.16±5.08 in the case group and 125.22±7.75 in the control group. Statistically significant difference exists in the SBP between the groups (p value≤0.05); the DBP was 79.48±3.17 in the case group and 79.91±2.82 in the control group; the PR was 80.56±5.20 in the case group and 84.40±5.65 in the control group. Statistically significant difference exists in the PR between the groups (p value≤0.05); the QRS (s) was 0.076±0.01 in the case group and 0.081±0.01 in the control group. Statistically significant difference exists in the QRS (s) between the groups (p value≤0.05); the ECG HR was 80.56±5.20 in the case group and 85.42±6.15 in the control group. Statistically significant difference exists in the ECG HR between the groups (p value≤0.05); the HR max was 140.52±3.41 in the case group and 115.12±10.28 in the control group. Statistically significant difference exists in the HR max between the groups (p value≤0.05) (Table 2).

Table 2: Comparison of the study variables.

Variables	Case	Control	p value
FT4	0.80±0.23	0.75±0.30	0.399
TSH	13.31±9.71	3.19±4.26	<0.001
Pre-TET MDA	18.74±6.56	3.30±0.72	<0.001
Post-TET MDA	20.62±6.56	5.45±0.89	<0.001
SBP	121.16±5.08	125.22±7.75	0.003
DBP	79.48±3.17	79.91±2.82	0.470
PR	80.56±5.20	84.40±5.65	0.001
QRS (s)	0.076±0.01	0.081±0.01	<0.001
ECG HR	80.56±5.20	85.42±6.15	<0.001
HR max	140.52±3.41	115.12±10.28	<0.001

Both FT4 and TSH showed positive correlation with post-TET MDA (r=0.0003 between FT4 & Post-TET MDA and r=0.5313 between TSH & Post-TET MDA) (Figure 1& 2). Comparison of stress levels with duration among the cases showed that, the highest stress level was found in new cases (29.18±0.92) and lowest was found in 1 year (15.06±4.64) and statistically significant difference exists between the stress levels in different durations (p value≤0.05). And comparison of pre-TET MDA and post-TET MDA in cases showed that, the pre-TET MDA was 18.74±6.56 and post-TET MDA was 20.62.12±6.57 in the case group and statistically significant difference exists between pre-TET MDA and post-TET MDA (p value≤0.05).

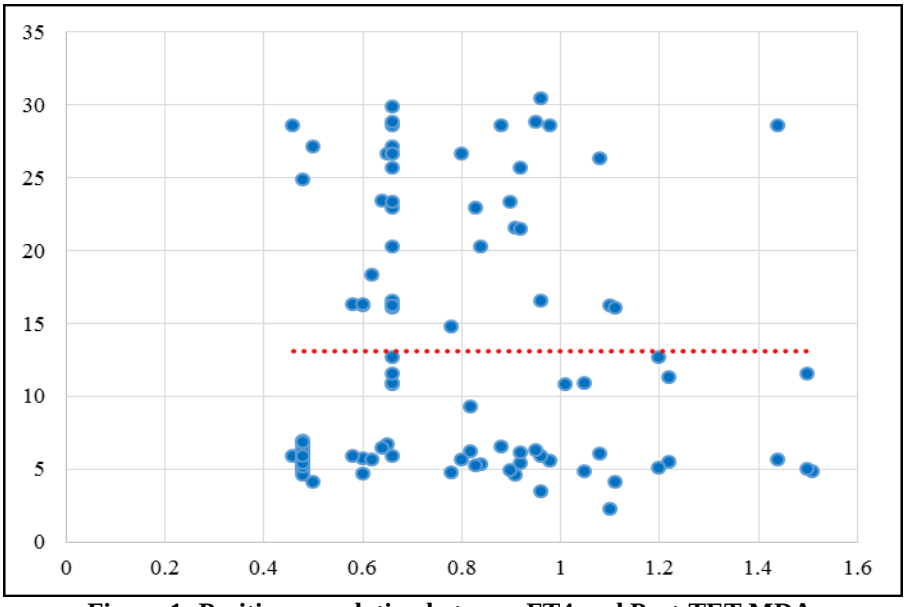

Figure 1: Positive correlation between FT4 and Post-TET MDA.

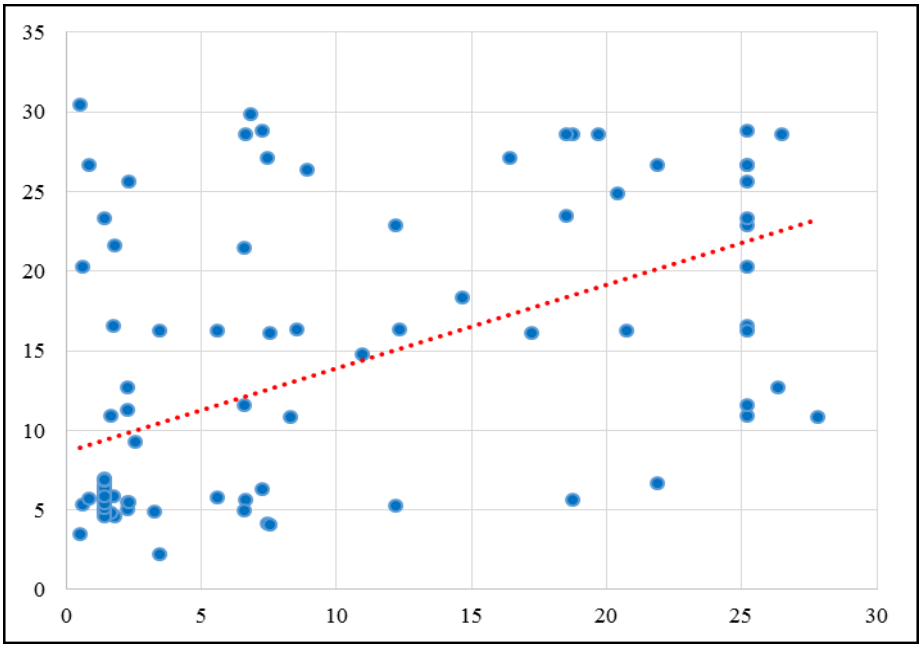

Figure 2: Positive correlation between TSH and Post-TET MDA.

DISCUSSION

The present case control study consisted of 50 patients and 50 healthy controls. The mean age of the cases were significantly higher than the mean age of the controls where the mean age was 30.38±4.61 years in the case group and 25.44±4.89 years in the control group. These findings are similar to the study by Huang et al.[11] showed the age of the patients was 23-27 years. The gender distribution in the present study showed female predominance in comparison to the male in both the groups where the case group had 26% male and 74 % female and the control group had 48% male and 52% female. Banshal et al10 also showed similar findings in case of gender distribution. The distribution of occupation of the participants showed that the mostly affected persons were housewives followed by students, labourers and drivers where the case group had 64% housewives, 4% drivers, 12% labourers and 20% students and the control group had 22% housewives, 8% drivers, 10% labourers and 60% students. The higher prevalence in the housewives can be justified as the predominant gender in the study was female and most of the adult females in a developing country like India are housewives. The distribution of socioeconomic status of the participants showed that the mostly affected persons were from low socioeconomic status in both the groups where the case group had 80% patients from low socioeconomic status and 20% patients from middle socioeconomic status and the control group had 98% patients from low socioeconomic status and 2% patients from middle socioeconomic status. The higher prevalence in the low socioeconomic status can be

justified as the physical and mental stress are usually higher in this section. Moreover not all from this socioeconomic level can afford proper treatment for thyroid disorder. Hence, thyroid dysfunction can be more frequently seen in them.

When the FT4 was compared between the case and the control groups, it was found that mean FT4 was higher in the case group in comparison to the control group where the mean FT4 was 0.80±0.23 in the case group and 0.75±0.30 in the control group. Similar results can be seen in the study by Anthony et al.[12] Although a slightly different result was reported in the study by Francisco et al.[13] where mean FT4 level was 0.95 in cases which was lower than that of 0.98 in controls.

When the TSH was compared between the case and the control groups, it was found that mean TSH was significantly higher in the case group in comparison to the control group where the TSH was 13.32±9.71 in the case group and 3.19±4.26 in the control group. Francisco et al.[13] reported that the case group showed higher TSH (5.58) in comparison to the controls (2.10). Fathi et al.[14] also reported that the case group had higher level of TSH than the control group.

When the pre-TET MDA was compared between the case and the control groups, it was found that mean pre-TET MDA was significantly higher in the case group in comparison to the control group where the pre-TET MDA was 18.74±6.56 in the case group and 3.30±0.72 in the control group. And when the post-TET MDA was compared between the case and the control groups, it was found that mean post-TET MDA was significantly higher in the case group in comparison to the control group where the post-TET MDA was 20.62±6.56 in the case group and 5.45±0.89 in the control group. The exercise increased the oxidative stress in the body that led to the rise of MDA levels in the persons of both the groups. But hypothyroidism resulted in the higher levels of MDA in the case group both in pre-treatment and post-treatment measurements. Similar results are reported in the study by Baskol et al.[15] where both pre-treatment and post-treatment levels of MDA was higher in the case group in comparison to the control group. Their study was designed to investigate the relationship between the serum levels of oxidant-antioxidant system (malondialdehyde (MDA) level, Paraoxonase (PON1) activity, nitric oxide (NO) level and superoxide dismutase (SOD) activity) and thyroid hormone status in hypothyroidism pre and posttreatment. The study group comprised 33 patients with primary hypothyroidism. 18 of these patients were re-evaluated after euthyroid state i.e. at least 6 months of thyroxine replacement. The patients were compared with 26 normal healthy controls. Serum MDA level, PON1 activity, NO level and SOD activity were measured according to an enzymatic spectrophotometric method. MDA levels were found higher in patients with hypothyroidism before the treatment than the controls. MDA levels were also found to be decreased after the treatment in patients with hypothyroidism. However MDA were found still higher than the controls after the treatment. PON1 activity was found to be lower in patients pre- treatment when compared to posttreatment hypothyroidism and controls. Posttreatment of hypothyroidism mean PON1 activity significantly increased compared to pre-treatment level but it was still significantly lower than control level.

The present study shows that there is a positive correlation between FT4 and post- TET MDA and a positive correlation between TSH and post-TET MDA. That means, oxidative stress as well as MDA levels will increase if there is any increase in the FT4 level and TSH level. In other words, increase in the FT4 and TSH can be observed if there is increased oxidative stress as well as MDA in the body. Baskol et al.[15] also reported similar correlation between the thyroid hormones and oxidative stress. It is a well-known fact that exercise affects the activity of many glands and the production of their hormones. One of the glands affected is the thyroid. It is also known that thyroid hormones act in fatty acid oxidation and thermoregulation. Thyrotropin-releasing hormone (TRH) secreted from hypothalamus stimulates anterior pituitary to release thyrotropin (TSH, thyroid stimulating hormone). When exercise is repeated at certain intervals, there is a pituitary-thyroid reaction that is properly coordinated by increasing turnover of thyroid hormones.[16-20]

CONCLUSION

It is most likely that many of the mechanisms participating in the development of thyroid pathologies are still unknown. However, there is a notable connection of increased reactive oxygen species generation and findings of oxidative damage with the development of thyroid cancer and other diseases described here. In addition, thyroid disorders may also initiate or increase ROS release and oxidative stress, enhancing oxidative damage. The most recent studies suggest a close link between thyroid diseases and oxidative stress. Taking into consideration research findings to date, it would appear that preventive nutrition therapy against redox imbalance, in enriching the daily diet in products with a high antioxidant value and supporting the internal antioxidant defence systems, may constitute a promising approach to preventing the development of many chronic thyroid diseases. This creates a prospect for developing measures precisely targeted at the free radical background, which can be used in the treatment and prevention of thyroid diseases as well as other oxidative diseases.

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