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Research Article

A CASE CONTROL STUDY ON EFFECT OF SMOKING ON THYROID HARMONES (T3&T4)

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ABSTRACT

Background:-Tobacco is the most common illicit psychoactive substances being used globally and is the biggest contributors to mortality and morbidity. Tobacco has multiple effects on the hypothalamic-pituitary-thyroid axis and the functioning of the thyroid gland.Smoking is the most common addiction in general population. Tobacco smoking is considered as the commonest source of toxic chemical exposure and chemically mediated illness in humans. It has varied effects on thyroid function. The effect of smoking on thyroid is believed to be due to the compound thiocyanate, a potent inhibitor of iodide transport, potentially capable of affecting the thyroid function. The aim of this study is to evaluate the thyroid hormones status in smokers. **Methods:** A case control study is done with 82 patients divided into 2 groups. Group 1 (healthy male non-smokers) as control and Group 2 (healthy male smokers) as cases with inclusion and exclusion criteria. Fasting blood samples were collected and serum T3 and T4 were measured. The data was analysed using unpaired t test. **Results:** In the present study significant increase in thyroid hormones T3 and T4 levels is observed in the cases compared to the controls. Mean±S.D of T3 and T4 in Group 1 is 1.077±0.3469, 8.745±1.215 and in Group 2 is 1.541±0.3644, 9.822±2.066 respectively, so there is a significant increase in the thyroid hormones of group 2. **Interpretations & Conclusion:** The finding in this study indicates that smoking is associated with increase thyroid hormones T3 and T4 in blood (biochemical hyperthyroidism). Hence evaluating thyroid hormone status in smokers might help in identifying occurrence of thyroid disorders and appropriate measures could be taken to prevent severity of morbidity and mortality associated with smoking.

Keywords :- Thiocyanate, hyperthyroidism, smoking.

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INTRODUCTION

India, as per WHO projection, will have the highest rate of rise in tobacco-related deaths during this period compared to all other countries/regions [1-3]. According to the National Family Health Survey (NFHS)-3 survey, conducted in 2005–06, tobacco use is more prevalent among men, rural population, illiterates, poor and vulnerable section of the society [4]. Youth in general and adolescents in particular fall prey to this deadly habit with severe physical, psychological, and economic implications [5]. India's tobacco problem is very complex, with a large use of a variety of smoking forms and an array of smokeless tobacco products. Many of these products are manufactured as cottage and small-scale industries using varying mixtures and widely differing processes of manufacturing [6].

Tobacco smoke contains around 7000 chemical compounds of which at least 158 compounds have been reviewed in scientific literature as harmful, carcinogenic, and/or potentially affecting physiological functions [7]. Tobacco smoke contains numerous compounds, the important substances of medical significance being the carcinogens (such as polycyclic aromatic hydrocarbons),

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irritant substances, nicotine, carbon monoxide and other gases [8]. The effect of cigarette smoke on thyroid is believed mostly to be due to the compound "thiocyanate" [SCN^-], Thiocyanate [SCN^-], a complex anion, is a potent inhibitor of iodide transport. It is the detoxification product of cyanide with a half-life of 10–14 days [9]. The relatively long biological half-life prevents large fluctuations in body fluids and enables accurate measurements in serum and urine. Since cyanide is generated from colonic bacteria, SCN^- is normally present in body fluids. Consumption of naturally occurring goitrogens, certain environmental toxins and cigarette smoke can significantly increase SCN^- concentrations to levels potentially capable of affecting the thyroid gland [10]. Thiocyanate [SCN^-] inhibits iodide transport and organification as well as increases the release of iodide from the thyroid. Thiocyanite [SCN^-] can cause goiter in iodine deficiency, while 2-3hydroxypyridine, a tobacco smoke toxin, inhibits thyroxin deiodination by reducing iodothyronin doiodenase activity [11]. This temporary effect mildly elevates serum thyroxin levels due to its deiodenase altering activity before reducing the levels [20]. Inhibition of iodide transport by thiocyanate is independent of TSH concentration but competitive with iodine concentration.

Cigarette smoking has multiple effects on thyroid function. These include both pro- (e.g. thyroid stimulating) and anti-thyroid actions and also actions that increase susceptibility to or exacerbation of the manifestations of Graves' disease.[14] Tobacco use is the single most important preventable health risk in the developed world and an important cause of premature death worldwide. Smoking causes a wide range of diseases including many types of cancer, chronic obstructive pulmonary disease, coronary heart disease, stroke, peripheral vascular diseases and peptic ulcer diseases [12,13].

The thyroid hormones are critical in cellular metabolism and in the coordination of physiological and behavioural responses (e.g., growth, maturation, and differentiation to biological stimuli). In women of reproductive age, thyroid hormone insufficiency can impact fertility and reproduction, resulting in pregnancy loss and low birth weight.

TSH is the major regulator of the morphologic and functional states of the thyroid. All steps in the formation and release of thyroid hormones are stimulated by TSH secreted by the pituitary thyrotrophs. Thyroid cells express the TSH receptor (TSHR), a member of the glycoprotein G protein–coupled receptor family. The effect of cigarette smoke on thyroid is believed mostly to be due to the compound "thiocyanate", a derivate of hydrogen cyanide with a half-life > 6 days [14-18]. Thiocyanate inhibits iodide transport and organification as well as increases the release of iodide from the thyroid. Thiocyanite can cause goiter in iodine deficiency, while 2-3hydroxypyridine, a tobacco smoke toxin, inhibits thyroxin deiodination by reducing iodothyronin doiodenase activity. This temporary effect mildly elevates serum thyroxin levels due to its deiodenase altering activity before reducing the levels [19,20]. Due to multiple contrasting pathways in which tobacco smoke can effect in the functioning of thyroid gland, individual cross sectional studies have reported a decrease and increase or no effect of smoking on peripheral thyroid hormones [21].

In normal adults, smoking has either a weak stimulatory or no effect on thyroid function and size. Small increases in thyroid hormones, mainly serum triiodothyronine and thyroglobulin concentrations may occur [22].

This present study will contribute to the existing knowledge of the detrimental effects of tobacco smoking on thyroid function by evaluating the thyroid hormone levels.

Materials and methods

Settings

A case control study was conducted in the Department of Biochemistry, Osmania General Hospital, Hyderabad.

Sources of samples and data

The cases and samples were collected from Department of General Medicine, Osmania General Hospital, Afzalgunj and Department of Biochemistry, Osmania General Hospital.

Cases

Healthy male smokers, a brief history was taken and samples were collected.

Investigations were performed at the Department of Biochemistry, Osmania Medical College / Osmania General Hospital.

Controls

Healthy male non-smokers, a brief history was taken and samples were collected and investigations were performed at the Department of Biochemistry, Osmania Medical College / Osmania General Hospital.

In the present study the individuals were divided into two groups.

Group 1	Healthy male non - smokers	N = 41
Group 2	Healthy male smokers	N = 41

Informed oral and written consent was taken from all individuals who took part in the study.

Inclusion criteria

1) Smokers 2) No history of thyroid disease 3) Healthy males 4) No history of any steroids medication 5) No history of liver disease 6) Age between 25 to 50 years 7) No pituitary disorders.

Exclusion criteria

1) Non – smokers 2) History of thyroid disease 3) History of consumption of steroids medication 4) History of liver

disease 6) Age less than 25 years and above 50 years 7) Patients with pituitary disorder

Specimen collection

4ml of Fasting venous blood were collected in a vacutainer (RED CAP). Sample was centrifuged at 3000 r.p.m for 10 minutes and serum was separated for analysis within two hours of collection of blood. Grossly haemolysed and lipemic samples were excluded.

The ethical issues involved in this study were reviewed and approved by the ethics scientific committee of Osmania Medical College.

Statistics analysis: The data was analysed using GraphPad prism 6.0

Methodology

T3 and T4 estimated by Method: ELISA (CALBIOTECH KIT) – TS227T [23]

T3 (Triiodothyronine)

Method: ELISA (CALBIOTECH KIT) – T3225T [23]

The CBI T3 is a solid phase competitive ELISA. The samples, T3 Antibody-Biotin Solution and the diluted T3 enzyme conjugate are added to the wells coated with Streptavidin. T3 in the patient's serum competes with a T3 enzyme (HRP) conjugate for binding sites. Unbound T3 and T3 enzyme conjugate is washed off by wash buffer during a wash step. Upon the addition of the substrate, the intensity of color is inversely proportional to the concentration of T3 in the samples. A standard curve generated relating color intensity to the concentration of the T3.

T4 (Thyroxine)

Method: ELISA (CALBIOTECH KIT) – T4224T [23]

The CBI T4 is a solid phases competitive ELISA. The samples, working T4-HRP Conjugate and Anti-T4-Biotin Solution are added to the wells coated with Streptavidin. T4 in the patient's serum competes with a T4 enzyme (HRP) conjugate for binding sites. Unbound T4 and T4 enzyme conjugate is washed off by washing buffer. Upon the addition of the substrate, the intensity of color is inversely proportional to the concentration of T4 in the samples. A standard curve is prepared relating color intensity to the concentration of the T4.

Results

The present study was undertaken in the department of Biochemistry Osmania General Hospital. A total of 82 male subjects of 41 subjects were smokers and 41 were non-smokers. Triiodothyronine and Thyroxin estimated according to the standard procedures and compare the results between smokers and non smokers.

The data was analyzed using Graph Pad prism Software version 6 and the results were expressed as Mean and Standard deviation of various parameters in different groups. The results were expressed in µIU/ml for serum TSH, Serum T3 in ng/ml and serum T4 in µg/dL The Mean ± SD of all the parameters studied in the total cases were significantly different from those of controls. The significance of different mean values of different groups is represented by P values and P values < 0.05 is considered as significant.

Table.1:Age of total study population (N = 82) i.e Group 1 and 2

MINIMUM AGE	MEDIAN AGE	MAXIMUM AGE
25.00	31.50	48.00

Thus the age range of the total study population is between 25 – 48 years

Table 2: Age of smokers in the smoking population study i.e Group 2

MINIMUM AGE	MEDIAN AGE	MAXIMUM AGE
25.00	32.00	48.00

Table 3: Age of non-smokers in the non-smoking population study i.e Group 1

MINIMUM AGE	MEDIAN AGE	MAXIMUM AGE
25.00	30.50	45.00

Table 4: Number of cigarettes smoked per day in a study population

MINIMUM	MAXIMUM	MEAN ± SD
3.00	40.00	12.17 ± 7.836

Table 5: Duration in years of cigarette smoking in a study population

MINIMUM	MAXIMUM	MEAN ± SD
3.00	25.00	12.02 ± 5.360

Table 6: Mean ± SD of studied parameters in all groups

Parameter	Group 1 (CONTROL)			Group 2 (CASES)		
	Mean	±S.D	SEM	Mean	±S.D	SEM
T3*	1.077	0.3469	0.05418	1.541	0.3644	0.05691
T4*	8.745	1.215	0.1898	9.822	2.066	0.3226

Table 7: Unpaired t test of T3 in 2 groups

P Value	T	df	Mean ± SEM of Group 1	Mean ± SEM of Group 2
<0.0001	5.900	80	1.077 ± 0.05418	1.541 ± 0.05961

Table 8: Unpaired t test of T4 in 2 groups

P Value	T	df	Mean ± SEM of Group 1	Mean ± SEM of Group 2
<0.0051	2.878	80	8.745 ± 0.1898	9.822 ± 0.3226

In the present study, Non-smokers had all the two parameters that is, T3 and T4 within normal limits. There were no significant changes all the parameters. They found in normal limits. The present study analyzed data on 82 men, of whom 41 were smokers and 41 were non-smokers. In this study the age range for the study population was 25 to 48 years. The minimum age is 25.00 years, median age is 31.50 years and the maximum age is 48.00 years of the total study population respectively. The numbers of cigarettes smoked in a smoking population is minimum 3 per day and maximum 40 per day and the duration of smoking was minimum of 3 years and maximum of 25 years.

The Mean ± SD of T3 was higher for smokers than non-smoker. The mean and median of T3 value in this study population is 1.309 and 1.345 respectively. The Mean ± SD of T4 was higher for smokers than non-smoker. The mean and median of T4 value in this study population is 9.284 and 9.026 respectively.

DISCUSSION

Thyroid gland is important in human body because of its ability to produce T3 and T4 hormones which are necessary for normal development of body organs, to maintain appropriate energy levels and an active life.[146] These hormones are required for normal growth, development and function of nearly all the tissues, with major effects on oxygen consumption and metabolic rate.[147] Thyroid hormone synthesis and secretion is regulated by a negative feedback system that involves the hypothalamus, pituitary and thyroid gland [24].

Within the thyroid gland, thyroid hormone synthesis requires iodine and the enzyme thyroid peroxidase to turn thyroglobulin (Tg) into thyroxine and triiodothyronine, T4 and T3, respectively. Thyroxine and triiodothyronine are then released into the bloodstream, where they are part of protein synthesis and metabolic processes in a multitude of cells and tissues. The regulation of thyroid hormones is a complex process. In a person with healthy thyroid function, the presence of excess or lack of iodine, for example, leads the thyroid gland to make and release more or less of its hormones. The level of hormone in circulation signals the suppression or the synthesis of other hormones like TRH and TSH that in turn help maintain thyroid hormone balance [25].

Cigarette smoking has multiple effects on thyroid function. These include both pro- (e.g. thyroid stimulating) and anti-thyroid actions and also actions that increase susceptibility to or exacerbation of the manifestations of Graves' disease [22].

The effect of cigarette smoke on thyroid is believed mostly to be due to the compound "thiocyanate", a derivate of hydrogen cyanite with a half-life of more than 6 days [14-18].

Thiocyanate has a molecular size quite close to that of iodide. It also demonstrates antithyroid activity in experimental studies where it has been extensively used to block the reuptake of iodide by the thyroid. Thiocyanate alters the iodine pump by inhibiting the oxidation of iodine and by inhibiting tyrosine iodination, effects that could lower circulating hormone level. Thiocyanate inhibits iodide transport and organification as well as increases the release of iodide from the thyroid [26, 27].

The effect of 2,3-hydroxypyridine is similar to that of propylthiouracil. Like propylthiouracil, 2,3-hydroxypyridine may slightly and temporarily elevate serum T4 levels as a consequence of its deiodinase-altering activity prior to decreasing these levels.

In the present study the Mean ± SD of serum T4 levels in Group 1 was 8.745 ± 1.215 and group 2 was 9.822 ± 2.066. The increase in serum T4 levels in group 2 was significant ($p < 0.0051$). This implied that smokers have abnormally high serum T4 levels when compared to controls. Due to certain environmental toxins and cigarette smoke which can significantly increase SCN− concentrations to levels potentially capable of affecting the thyroid gland. Thiocyanate [SCN^-] inhibits iodide transport and organification as well as increases the release of iodide from the thyroid.

These findings were in concordance with the following studies. Study conducted by Chester L fisher et al showed significantly higher serum T4 levels among current smokers than among former smokers and never smokers [20]. Increase in T4 was thought to be related to a decrease in thyroid-binding globulin that was associated with androgen therapy.

In the present study we compared the Mean ± SD of serum T3 levels in Group 1 was 1.077 ± 0.3469 and Group 2 was 1.541 ± 0.3644. The increase in serum T3 levels in Group 2 was significant ($p < 0.0001$). This implied that smokers have higher serum T3 levels compared to controls. It can be assumed that the increase in T3 levels was resulting from either enhanced production or reduced clearance. A constituent of tobacco smoke, benzpyrene is known to induce hepatic conversion of T4 to T3 which is stimulated due to hepatic oxidative metabolism. These studies agreement with the previous studies done by Karakaya A et al, also observed high serum T3 levels in heavy smokers than those of non-smokers. This, finding supports the view that smoking can stimulate the extrathyroidal conversion of T4 to T3 [14]. A possible mechanism could be enhanced activity of the hepatic oxidative system, induced by benzpyrene in smoke [28,29,30]

This was similar to study by Christensen SB et al. They found higher serum T3 levels in heavy smokers than never smokers. It can be assumed that the increase in T3 was resulting from either enhanced production or reduced clearance [31]. This finding emphasizes the possibility that there are both transient and sustained effects of smoking and cessation of smoking on thyroid hormone economy.

In the present study, there is increase in T3 and T4 levels in male smokers with non-smokers. These findings indicates that there is a state of biochemical hyperthyroidism in smokers as compared to non-smokers. Identification thyroid hormone status in smokers might help in predicting occurrence of thyroid disorders and appropriate measures could be taken to prevent severity of morbidity and mortality associated with smoking. In addition to TSH, T3 and T4 for predicting thyroid disorders in smokers, some useful biomarker (thyroid peroxidase) analysis essential for the predicting the thyroid disorders.

CONCLUSION

In case control study, there was significant variation in T3 and T4 levels in both smokers and non smokers. There was a elevation of these two thyroid harmones in smokers cases will lead to the development of Hyperthyroidism.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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