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A Survey on Thyroid Hormonal Status among Moderate to Severe Stable Chronic Obstructive Pulmonary Disease

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ABSTRACT

Background: COPD is one of the common diseases in pulmonary medicine. Current knowledge indicated that there was a link between COPD with thyroid hormonal abnormalities. Thyroid function disturbances can be able to affect on the COPD through upper airway obstruction, respiratory muscle weakness, development of central and obstructive sleep apnea, alveolar hypoventilation, and pleural effusion. Thyroid abnormalities are often both detectable and treatable. The aim of the study is to assess serum levels of thyroid hormones among moderate to severe stable COPD patients.

Methods: 34 men were enrolled consecutive among established and stable COPD patients with moderate to the severe stages. Their selection constructed on the ATS/GOLD guidelines. Thyroid functions and hormonal concentrations measured according to manufacturer's instructions.

Results: Mean age of sample was 51.7±5.76 SD years. It ranged over 42–60 years (Mode=49). Significant thyroid hormonal abnormalities were detected among established moderate to the severe COPD patients. The mean±SD of TSH, TT4 and free T3 concentrations in the focus population was 2.36±1.53 microIU/ml, 12.15±2.15 Micro/dl and 2.20±0.45 pg/ml, respectively. Frequency distribution of thyroid disorders included euthyroid functions 76.5%; three subjects of those had euthyroid sick syndrome, subclinical hyperthyroidism 20.6% and over hypothyroidism 2.9%, respectively. Grades of goiter on WHO classifications observed 0=44% and 1=41%.

Conclusion: Frequent exacerbations of thyroid disorders were detected among stable, moderate to severe COPD patients. Subclinical hyperthyroidism and euthyroid sick syndrome were significant. Despite that prevalence of hypothyroidism is considerable in age-rang of Iranian's population.

►*Implication for health policy/practice/research/medical education:* Thyroid Hormonal Status among Moderate to Severe Stable Chronic Obstructive Pulmonary Disease

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1. Introduction:

Abnormalities in thyroid hormones concentrations have been observed in critical and can couse long-term systemic disease (1). Chronic obstructive pulmonary disease (COPD) is the chronic inflammatory airways' diseases of unknown etiology. It is characterized by partially reversible or fully irreversible airflow obstruction (2).

COPD influenced on the thyroid hormonal regulation via etiologic causal factor and nature of disease. Tobacco smoke is considered the main risk factor of developing COPD (3). Current reports demonstrated that smoking was really associated with risks of both non-toxic, toxic goiter (4-6) and thyroid hormone abnormalities (7). In addition, COPD has noticeable extra-pulmonary manifestations, the so-called systemic effects of COPD (8). It comprises inflammatory mediators, hypoxemia originated in advanced disease and chronic systemic effect (9).

Hypothyroidism and hyperthyroidism are diagnostic diseases and treatable causes. Thyroid dysfunction has been influential known effects on respiratory system, including upper airway obstruction, respiratory muscle weakness, central and obstructive sleep apnea, alveolar hypoventilation, and pleural effusion (10). All of these clinical features contributed on developing complications in COPD patients. However, the concept of the present study limited to the literature review.

The aim of the study assessed status of thyroid hormonal status among moderate to severe stable COPD patients.

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2. Materials and Methods:

The study was cross–sectional, descriptive. It finalized in Shahid Beheshti University of Medical Sciences (SBUMS), Logman Hakeem general teaching hospital, pulmonary division, Tehran-Iran, 2007.

Initially, COPD suspected if the patients had symptoms such as, dyspnea, cough, and or sputum production as well as to possess history of cigarette smoking. Then all patients followed with accepted definition of diseases and standard pulmonary function test (PFT), chest standard radiography, arterial blood gas and electrocardiograms. Two-dimensional echocardiography utilized for confirmation of congestive heart failure.

Diagnostic confirmation of the COPD was mad according to documented criteria with Global Initiative for Chronic Obstructive Lung Disease (GOLD) (11) and American thoracic Society (ATS) (12). COPD disease nearly all refers to chronic bronchitis and emphysema. Chronic bronchitis defined by the persistent or recurrent sputum production on the most days up to a minimum of three months per annum, at least two consecutive years. It does not contribute to any other, pulmonary or cardiac and tuberculosis diseases (13).

Confirmation of reversibility of airway obstruction documented with applying a standard post–bronchodilator test. Spirometric parameters determined forced expiratory volume in first second (FEV1), forced vital capacity (FVC), and ratio of FEV1 to FVC. Cut-off points of spirometric values were FEV1, FVC equated or less than 80% and FEV1 /FVC ratio<70% predicted (11). The highest value from at least of tree trial's maneuvers of FEV1 and FVC utilized for

statistical analysis. Complete reversibility of airways, obstruction described with a response to standard bronchodilator test nebulization. Accepted criteria is increasing FEV1 up to or equal 12% or volume changes>200 ml (11). PFT performed at sitting position and in the morning. The instrument using was the sensor medics 2002 made by the care cardiopulmonary company.

Puls-oximetry carried out at sitting position prior to the PFT. Arterial blood gas samples obtained while the subjects were breathing room air (20 minute).

Grade of using smoking was on subsequent; No current daily smoking G=0, current smoking less than 10 cigarettes per day G=1 and more G=2 (14).

The severity of COPD had been diagnosed by a respiratory physician based on a documented guideline (15). It categorized as moderate: 50 %< FEV1<80% and sever: FEV1 <50% Predicted value.

In second step, the physician examined all the COPD patients. Goiter if presented it graded according to the World Health Organization (WHO) criteria. They consisted of conditions; a non-palpable thyroid tissue as grade 0, palpable but non-visible goiter as grade 1 and palpable and visible goiter as grade 2 (16).

Body Mass Index (BMI) calculated from the height to body weight in kg. Normal range was 19 and 25 (17). Decreasing in BMI level reported in COPD patients due to systemic inflammation and oxidative stress (18).

Patients do not meet criteria of study excluded. Those consisted of taking oral glucocorticoids or any known drugs to affect thyroidal function namely; amiodarone, iodine-containing contrast media, current use of thyroid medication. Those had clinical or diagnosed evidence of thyroid diseases, recent exacerbation or hospitalization within the four weeks prior to the study. However, known medical illness can effect on thyroid functions such as; surgery on the thyroid gland, renal, malignancy, neuromuscular, hepatic and collagen diseases. All patients gave their informed consent.

All patients used inhaled β2-agonist and inhaled steroid. Medications program among COPD patients included inhaled salmeterol: seventeen (21%), formoterol: 14 (12%), salbutamol: ten (30%), fluticasone: 16 (47%), beclomethasone: eight (23%), oral prednisolone: four (12%), ipratropium bromide: twenty (59%), tiotropium: eleven (33%), oral theophylline: seven (21%), furosemide (40mmg): five, spironolactone (75 mg): four cases.

Serum concentration of thyroid hormones analyzed with using electrochemiluminescence immunoassay. Venous blood obtained with supine position at the same morning for hormone analysis. Thyroid hormone measurements performed once and at unique laboratory.

The normal value in our laboratory was as follows; Thyroid stimulating hormone (TSH): 0.4-6.21 micro IU/mL, Total thyroxin (TT4): 4.7-12.5 Micro/dl, free T4: 0.7-1.8 ng/dl, triiodothyronine (TT3): 0.6-2.1 ng/ml, free T3: 2.2-4.2pg/ml, T3 resin uptake (T3 up): 25-35%, free thyroxin index: 1.05-4.20. TT3/TT4 ratio has been proven a useful tool in studying the peripheral conversion of thyroxine to triiodothyronine in various disease states.

The kits used for TSH ELIZA assay (MONOBIND, INC. Costa Mesta, CA 92627USA thyrotropin product cod 325-300). Thyroidal hormones were ELIZA assay (Pishtazteb ELIZA Kit). The diagnoses of thyroid states confirmed according to the reference criteria (19).

Statistical analyzing performed with SPSS software 16. Data presented as mean±standard deviation. Independent Sample-T test and Chi-square test used for comparisons of means. Statistical significant was set in $P<0.05$.

3. Results:

A total of 34 patients completed criteria of study. The mean±standard deviation of age was 51.74±5.76 years. It ranged over with 42 to 60 years, (mode=49). Table 1 shows

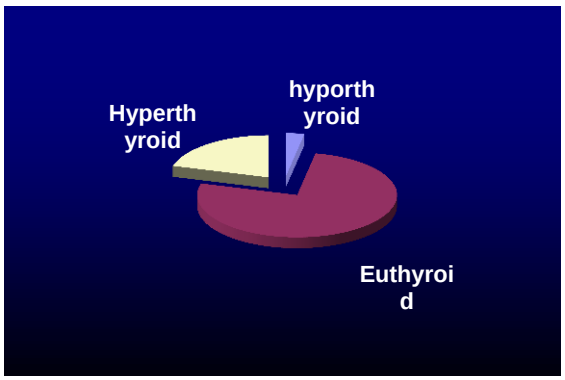

Fig. 1. It shows thyroidal diseases between COPD patients with stable condition.

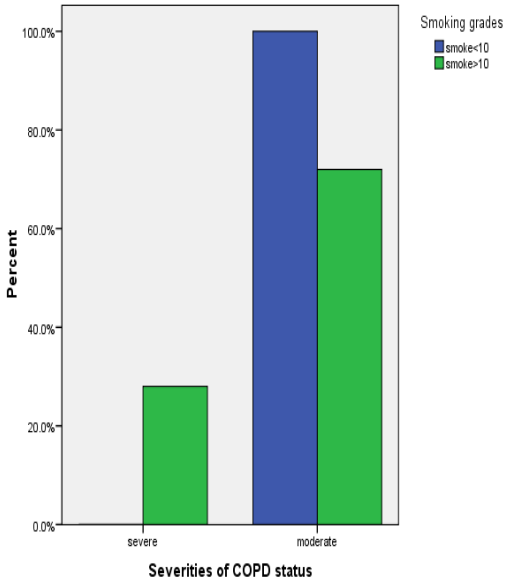

Fig. 2. It shows frequency distribution of COPD severities status with smoking using grad.

thyroid hormonal functions in the stable COPD patients.

Figure 1 disclosed distribution of thyroidal diseases among sample population. Thyroid hormone abnormalities observed including; Euthyroid state 26 (76.5%), subclinical hyperthyroidism 7 (20.6%) and overt hypothyroidism 1 (2.9%). Three subjects of the euthyroid state subset had euthyroid sick syndrome. Signs and symptoms of thyroid dysfunction clinically considered as lethargy, weight gain, hair loss, dry skin, forgetfulness, constipation and depression. Recent features did not find between samples of study. Overt clinical manifestations of COPD might be blunted features of thyroidal disease.

Frequency of grade's distribution of goiter included grade 0: fifteen (44.1%), grade1: fourteen (41.2%), grade 2: five cases (14, 7%), respectively.

Stage of severity in COPD sample was twenty-seven (79%) in moderate and seven (21%) at sever stages. Hormonal abnormality detected in thyroid functions of stable COPD patients with moderate severity as follow. TSH, TT4, FT4, TT3 and FT3 were 2.31±1.42 SD, 12.15±2.17 SD, 1.60±0.42 SD, 2.25±0.49 SD and 2.8±0.58 SD, individually. Abnormal thyroid functions in sever stage of COPD subset consisted of TSH: 2.56±2 SD, TT4: 12.11±2.27 SD, FT4: 1.72±0.35 SD, TT3: 2.01±0.21 SD and FT3: 2.52±0.50 SD. Independent sample T test performed between severities of COPD status with serum thyroidal hormonal concentrations. There was not meaningful relation.

Means of TT3/TT4 ratio recorded 0.23±0.18 SD. There was relevant difference between normal and high ratio ($P<0.001$). No significant difference observed between severity of airway obstruction with the recent ratio of peripheral hormone conversion ($P=0.96$). In addition, correlation found between PaO2 with TT3/TT4 ratio ($r=0.07$, $P=0.9$).

Frequency of smoking grades consisted of nineteen subjects (26%) at G=1 and twenty cases (74%) at G=2. Noticeable differences did not detect between smoking grades with thyroidal hormonal concentrations. Aside, no statistically significant differences found between severities of COPD and grades of the current smokers ($\chi>0.05$). Figure2 shows severities' distribution COPD status respect to using smoking grades.

Mean Pao2 was 85.44±3.62 SD mmHg. A significant difference found between severity of COPD status with Pao2 levels ($P<0.001$). There was a relevant correlation between FEV1 and PaO2 ($r=0.7$, $P=0.001$).

Mean BMI was 28.38±3.77 SD and nearly twenty-seven percentage (9/34) of patients had BMI in the normal range.

Table 1: It is showing incidence of violent asphyxial deaths.

	Target population
TSH micro IU/mL	2.36 ±1.53
Total T4 Micro/dl	12.15±2.15
Free T4pg/dl	1.62±0.40
T3ng/ml	2.20±0.45
T3 resin uptake%	34.12±2.56

Table 2: It presents characteristics of thyroid hormonal concentrations in cases and a control groups.

	Case	Control	P value
Number	34	56	
Total T4	12.15 ± 2.15	9.32 ± 2.0	0.001
TSH	2.36 ±1.53	3.06 ± 1.59	0.047
TT3	2.20 ± 0.45	1.65± 0.37	0.001
TT3/TT4	5.56 ± 1.23	6.08 ± 2.60	0.27

4. Discussion:

The outcome in the present study support thyroid hormonal abnormalities among selected population of COPD patients with stable condition. Meaningful subclinical hyperthyroidism and euthyroid sick syndrome detected respect to hypothyroidism. Link between COPD with thyroid diseases recognized so far as in recent years. COPD as a disease had several distinct effects on the thyroid gland functions such as; hypoxemia is a systemic effect of COPD, using tobacco smoke and chronic course of disease. Consequence of the study may be interpreted with following.

Tobacco smoke affects the various metabolic and biological processes within the body suchlike secretion of hormones. Cigarette smoking has both inhibitory and stimulatory action on the thyroidal functions. It reduces thyroid secretion in subclinical hypothyroidism and also, exacerbates peripheral effects of hormones in overt hypothyroidism. However, mild elevation of TSH accepted among smoker population as a smoker effect without clinical features of thyroidal disease (20).

Smoking enables to raise Triiodothyronine (T3) levels (21). It reflected effect of smoking on the hormonal concentration and agrees with other's study.

Thiocyanate and 2, 3-hydroxypyridine are toxins. They found in the tobacco smoke (22). 2-Amino-3-hydroxypyridine causes decreasing iodothyronine deiodinase activity, and leads to elevate serum thyroxin concentrations (T4) (23).Current data improves with medical evidence. Thiocyanate has a potential goitrogenic effect on iodide deficiency condition (24). General population of Iran has susceptible conditions of iodide deficiency (25, 26). Thiocyanate production via smoking habit may be consistently presented in case study group. Consequently, significant goiter observed in COPD patients (overall 29%).

Another risk factor should be considered the highlight of hypoxemia. Following evidence achieved in searching medical data-base. An abnormality of hypothalamic-pituitary function has been reported in hypoxic male patients (27). Basal and stimulated TSH reduced in severe airway obstruction (28). Changes of FT3 reported on COPD patients (29). However, severe nocturnal hypoxemia also enables to affect on thyroid function among COPD patients (30). Uniform results did not detect in cyanotic

congenital heart disease, although both illnesses had almost similar hypoxic condition (31). These changes have closely correlation with the activation of pro-inflammatory mediators, and inflammatory cytokines (32). Five subjects of sample population were receiving oxygen therapy at night. It indirectly reflected nocturnal hypoxemia. However, ABG data disclosed presence of hypoxemia in the early subset patients.

Euthyroid Sick syndrome (ESS) or non-thyroidal illness (NTI) meets defined criteria among three cases in COPD patients. Medical evidence showed that chronically an illness conditions such as COPD can be able to alter endocrine activity; thyroid function test and metabolic of the body (33, 34). Common thyroidal hormonal abnormalities enclosed declining totality triiodothyronine (TT3) and free triiodothyronine (FT3), normal or decreasing total thyroxine (TT4) and free thyroxine (FT4) (33). However, TSH concentrations are variable in the routine range. Recent condition of thyroid hormonal abnormalities has been known (ESS) or (NTI) (35). Lowest level of serum TT3 is the most common abnormality in NTI. It observed in about 35–70% of hospitalized patients (36). Low serum T3 and/or T4 levels were causality of increasing mortality from diseases such as cirrhosis and advanced congestive heart failure (37, 38).

Medical epidemiological evidence indicates that hypothyroidism and COPD are the common problems in internal medicine. COPD is the third- leading cause of death in the world by the 2020 year. Knowledge of hypothyroidism shows that prevalence of disease is significant in general population. The incidence of spontaneous overt hypothyroidism was 0.6/1000/year in mal sex (39). In addition, hypothyroidism and higher stages of COPD become increasingly common with old age. It is 2% in population. Our finding disagrees with the recent concept.

According to the published data, aging had significant effects on thyroid gland and functions. It causes declining mean TSH and T3 in serum without change in the T4 (40). Age Mode of study statistically situated in class of fourth decade. Its effect on the current data seems to be minimal.

Our study indicates considerable frequency of subclinical hyperthyroidism within COPD patients. Clinical effects of hyperthyroidism were not completely understood on the respiratory function, particularly in COPD patients. Literature reviewed information focused on the shortness of breath secondary to increase minute ventilation due to stimulation of the respiratory drive, reversible respiratory muscle weakness (41). Cardiovascular effects encompassed increased left ventricular mass, increased systolic function, and impaired diastolic function (42). Potential cause of low TSH concentrations may be suggested concerned to using high doses of glucocorticoids. It mimics subclinical hyperthyroidism (43). Inhalation history of glucocorticoid was managed among COPD patients. Our study limited for evaluation of hyperthyroidism etiology.

In conclusion, Considerable frequency of thyroidal disorders detected among stable, moderate to severe COPD patients. Subclinical hyperthyroidism and euthyroid sick syndrome was noticeable. Despite that, marked prevalence of hypothyroidism observed between age and rang of Iranian's population

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