ORIGINAL ARTICLE ASIAN JOURNAL OF MEDICAL SCIENCES

Association of thyroid function and obesity with chronic obstructive pulmonary disease: An observational cross-sectional study

Deepak Singh[1], Anjuman Chaudhary[2], Atul Kumar Singh[3], Abhishek Singh[4]

[1]District TB Officer, Amethi, [2]Associate Professor, Department of Community Medicine, RDASMC, Ayodhya, [3]Senior Resident, Department of Pulmonary Medicine, Autonomous State Medical College, Etah, [4]Assistant Professor, Department of Pulmonary Medicine, MLN Medical College, Prayagraj, Uttar Pradesh, India

Submission: 11-06-2023 Revision: 29-09-2023 Publication: 01-11-2023

ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD), defined by GOLD as a preventable and treatable disease with some significant extra pulmonary effects, is a very common clinical entity in clinical practice. COPD is associated with significant extra pulmonary (systemic) effects. Systemic inflammation may be mainly driven by risk factor – cigarette smoking and it persists after smoking cessation. COPD is associated with severe extrapulmonary (systemic) manifestations and comorbidities such as cardiac, osteoporosis, gastroesophageal reflux disease, Thyroid Dysfunctions, and obesity. Body mass index (BMI) has also been identified as an independent prognostic factor for COPD. **Aims and Objectives:** This study was conducted to determine the proportion of hypothyroidism and obesity in COPD patients and their association with GOLD stage. **Materials and Methods:** This was an observational cross-sectional study assessing, COPD patients to determine proportions of thyroid disorder and obesity within a period of 1 year. Data were coded and recorded in MS Excel spreadsheet program. SPSS v23 (IBM Corp.) was used for data analysis. **Results:** The following variables were significantly associated ($P<0.05$) with the variable "GOLD Stage: Weight (kg), BMI, and obesity. 30 (35.3%) COPD patient having abnormal thyroid profile and all 30 (35.3%) were diagnosed as hypothyroid. **Conclusion:** From the study, it was found that BMI of patient decreases with increase in GOLD COPD staging. This indicates that obesity might have some protective effect in COPD but this need to be further evaluated.

Key words: Obesity; Thyroid dysfunction; Chronic obstructive pulmonary disease; Hypothyroid

Access this article online

Website: http://nepjol.info/index.php/AJMS

DOI: 10.3126/ajms.v14i11.55662

E-ISSN: 2091-0576

P-ISSN: 2467-9100

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the major respiratory.[1] Non-communicable disease (NCD) persistent, low-level, systemic inflammation is thought to play a significant pathogenic role in many NCDs including COPD.[2] It is found that in COPD patients there is persistent elevated levels of white blood cells, C-reactive protein, interleukins 6 (IL-6) and 8 (IL-8), fibrinogen, and tumor necrosis factor alpha.[3]

The inflammation has an impact on other systems, for example: Cardiovascular, skeletal muscle, endocrine system, skeleton, and brain.[4,5]

Thyroid hormones play an important role in the regulation of thermogenesis and metabolism. During systemic illnesses, serum thyroid hormone level changes and so in respiratory diseases also.[6] Hypothyroidism may also cause alveolar hypoventilation, decreased lung volumes, upper airway obstruction, depression in respiratory stimulus, and respiratory failure. Hypoxia and decreased ventilator response to hypercapnia have been demonstrated in patients with hypothyroidism.[7,8] Diaphragmatic dysfunction and myopathies can be seen in patients with hypothyroidism. Inspiratory and expiratory muscle strength is linearly related to the degree of hypothyroidism.[7,8] The myopathic manifestations may be related to the impaired expression

Address for Correspondence:
Dr. Anjuman Chaudhary, Associate Professor, Department of Community Medicine, Rajarshi Dashrath Autonomous State Medical College, Ayodhya - 224 133, Uttar Pradesh, India. **Mobile:** +91-8005456988. **E-mail:** nutan237@gmail.com

of myosin heavy chains IIb or to impaired neuromuscular transmission.[9] Weakness correlates with the severity of hypothyroidism and is reversed by replacement therapy. Probably impaired muscle energy metabolism, resulting from a defect in glycogen breakdown or mitochondrial function and hypothyroid myopathy, contributes to the reduced exercise capacity in COPD patients. Hypoxia and hypercapnia cause destruction in sella turcica and pituitary gland dysfunction. Impaired thyroid function in COPD may present as subclinical hypothyroidism (ScH), overt hypothyroidism, and nonthyroidal illness syndrome. Furthermore, hyperthyroidism may impair respiratory muscle function and exercise in COPD patients. In fact, both maximal inspiratory pressure and expiratory pressure decrease, with increasing severity of hyperthyroidism. In several studies, it is seen that thyroid disorder is a common manifestation of COPD, and among which propensity of hypothyroidism is more than hyperthyroidism.

Systemic consequences, now recognized as important features of the disease (COPD), contribute to exercise intolerance, decreased health status, and increased mortality.[10] Among the most extensively studied systemic features are unexplained weight loss, alterations in the body mass index (BMI) and in body composition. Data from epidemiologic studies have shown that the prevalence of COPD is higher in those patients with lower BMI.[11,12] In addition, results from longitudinal studies have shown that low BMI is an important risk factor for subsequent development of COPD in men, for increased forced expiratory volume in 1 s (FEV1) decline in the same gender and for having a new exacerbation in patients hospitalized for severe exacerbation.[13]

BMI has also been identified as an independent prognostic factor for COPD, with a clear association between decreased BMI and increased mortality both in clinical patient series and in subjects from a population sample.[10] Several studies indicate that the prevalence of nutritional abnormalities increases from 20% in stable outpatients up to 35% in patients eligible for pulmonary rehabilitation. To date, most studies concerning the prevalence of nutritional depletion in COPD have been performed in selected populations. In general, they found that the prevalence of nutritional depletion in COPD was high, especially in females, and was not associated with lower levels of airway obstruction. Population-based studies are necessary because they represent more accurately the total spectrum of patients with the disease, thus allowing unbiased inferences. This study was done with following aims and objective to determine hypothyroidism on the basis of thyroid function test (TFT) and obesity on the basis of BMI, in patients of COPD and the proportion of hypothyroidism and obesity in COPD patients.

Aims and objectives

This study was done with following aims and objective to determine hypothyroidism on the basis of Thyroid Function Test and Obesity on the basis of BMI, in patients of COPD and the association of hypothyroidism and Obesity with Chronic Obstructive Pulmonary Disease (COPD) Patients.

MATERIALS AND METHODS

Study design

This was an observational cross -sectional study assessing, COPD patients to determine proportions of thyroid disorder and obesity within a period of 1 year.

Subjects

The present study was carried out in a teaching hospital during the year 2020–2021 at the Department of Pulmonary Medicine. All the patients of COPD attending the outpatient department (OPD) and admitted in inpatient department in Department of Pulmonary Medicine were eligible for getting enrolled in this study and these patients were investigated for TFT and Anthropometric parameters to determine BMI and obesity, with detailed clinical history and physical examination.

Case selection

1. Patients were enrolled in this study as per inclusion and exclusion criteria
2. Diagnosis of COPD was according to GOLD guideline 2019
3. Classification of COPD Patients according to GOLD guideline 2019
4. Classification of thyroid disorder on the basis of Serum FT3, Serum FT4, serum thyroid stimulating hormone (TSH)
5. Classifying patients as overweight and obese on the basis of BMI as per the WHO criteria.

Inclusion criteria

The following criteria were included in the study:

1. All patients of COPD attending OPD in department of pulmonary medicine SRN hospital Prayagraj (Allahabad)
2. All COPD patients admitted in the department of pulmonary medicine
3. Patients with FEV1/forced vital capacity ratio <0.7.

Exclusion criteria

The following criteria were excluded from the study:

1. Patients unable to perform PFT
2. Patients not giving consent
3. Patients with HIV
4. Patients with chronic disease other than COPD

5. Patients with history of previous thyroid surgery
6. Patients on any regular medication other than COPD drugs that might affect thyroid functions, for example, iodine containing drugs, amiodarone, and immunosuppressive drugs.

Study procedure

After obtaining written informed consent, patients qualifying inclusion criteria were assessed as follows:

- Recording of demographic data
- All patients of COPD were subjected to detailed history including history of smoking
- All patients of COPD were classified according to GOLD guidelines 2019
- In our study, thyroid disorder was determined by taking venous blood sample in the morning after 8 h fasting, and then biochemical examination (CMIA)[14] of blood sample for Serum FT3, Serum FT4 and Serum TSH
- In our study, obesity was defined and classified on the basis of BMI as per the WHO criteria.

Investigations

All enrolled patients were investigated for following parameters

1. Serum Free T3
2. Serum Free T4
3. Serum TSH
4. Spirometry
5. Chest X-ray PA view.
6. ECG
7. Anthropometric measurements
8. Others.

Statistical analysis of data

Data were coded and recorded in MS Excel spreadsheet program. SPSS v23 (IBM Corp.) was used for data analysis. Descriptive statistics were elaborated in the form of means/standard deviations and medians/IQRs for continuous variables, and frequencies and percentages for categorical variables. Group comparisons for continuously distributed data were made using independent sample "t"-test when comparing two groups. If data were found to be non-normally distributed, appropriate non-parametric tests in the form of Wilcoxon Test were used. Chi-squared test was used for group comparisons for categorical data. In case the expected frequency in the contingency tables was found to be <5 for >25% of the cells, Fisher's exact test was used instead. Statistical significance was kept at $P<0.05$.

Ethics

Institutional ethics committee permission was obtained before the start of the study.

RESULTS

A total of 85 COPD patients aged above 18 years were enrolled over a period of 12 months as per inclusion and exclusion criteria. They were classified into stages 1, 2, 3, and 4 as per GOLD guideline 2019. The male female

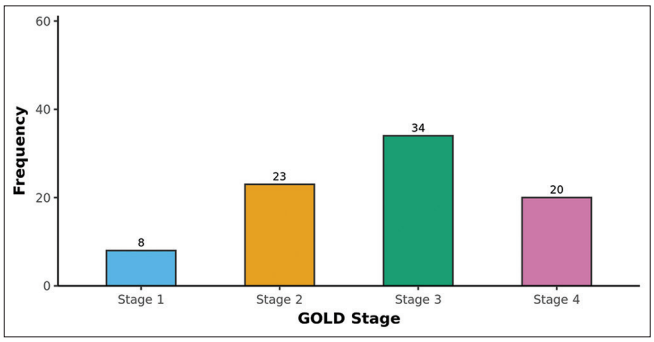

Figure 1: Distribution of GOLD stage

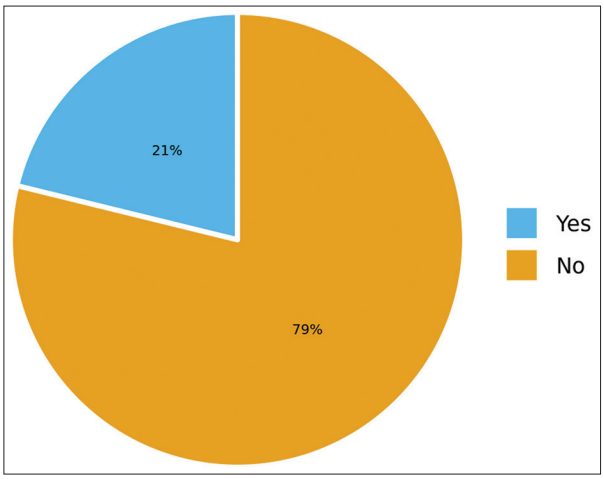

Figure 2: Distribution of obese

Table 1: Summary of basic detail

Basic details	Mean±SD||Median (IQR)|| Min–Max||Frequency (%)
Age (years)	60.82±7.43||60.00 (55.00–66.00)|| 45.00–78.00
Age	
41–50 years	7 (8.2)
51–60 years	40 (47.1)
61–70 years	31 (36.5)
71–80 years	7 (8.2)
Gender	
Male	60 (70.6)
Female	25 (29.4)
Smoker (yes)	58 (68.2)
GOLD stage	
Stage 1	8 (9.4)
Stage 2	23 (27.1)
Stage 3	34 (40.0)
Stage 4	20 (23.5)

The mean age (years) was 60.82±7.43

Table 2: Association between GOLD stage and parameters

Parameters	GOLD stage				P-value
	Stage 1 (n=8) (%)	Stage 2 (n=23) (%)	Stage 3 (n=34) (%)	Stage 4 (n=20) (%)	
Age (years)	62.25±8.35	60.91±7.30	61.32±8.07	59.30±6.32	0.768[1]
Age					0.480[2]
41–50 years	1 (12.5)	1 (4.3)	4 (11.8)	1 (5.0)	
51–60 years	2 (25.0)	13 (56.5)	14 (41.2)	11 (55.0)	
61–70 years	3 (37.5)	8 (34.8)	12 (35.3)	8 (40.0)	
71–80 years	2 (25.0)	1 (4.3)	4 (11.8)	0 (0.0)	
Gender					0.993[3]
Male	6 (75.0)	16 (69.6)	24 (70.6)	14 (70.0)	
Female	2 (25.0)	7 (30.4)	10 (29.4)	6 (30.0)	
Smoker (Yes)	4 (50.0)	14 (60.9)	26 (76.5)	14 (70.0)	0.408[3]
Weight (kg)***	64.88±11.70	55.52±10.15	52.29±7.23	54.85±6.41	0.028[1]
Height (cm)	159.38±8.48	160.04±7.40	160.82±6.64	158.15±6.24	0.469[1]
BMI (kg/m^2)***	25.41±3.26	21.71±3.47	20.42±3.74	21.70±2.58	0.010[1]
BMI***					<0.001[3]
<18.5 kg/m^2	1 (12.5)	6 (26.1)	17 (50.0)	3 (15.0)	
18.5–22.9 kg/m^2	0 (0.0)	8 (34.8)	7 (20.6)	12 (60.0)	
23.0–24.9 kg/m^2	0 (0.0)	4 (17.4)	6 (17.6)	3 (15.0)	
25.0–29.9 kg/m^2	7 (87.5)	5 (21.7)	4 (11.8)	2 (10.0)	
Overweight/Obese (Yes)***	7 (87.5)	9 (39.1)	10 (29.4)	5 (25.0)	0.012[3]
Obese (Yes)***	7 (87.5)	5 (21.7)	4 (11.8)	2 (10.0)	<0.001[2]
MUAC (cm)	22.75±2.82	23.91±2.79	23.53±2.56	23.50±2.98	0.699[1]
Neck circumference (cm)	33.88±2.23	34.00±2.75	33.38±2.71	34.00±2.53	0.965[1]
Waist circumference (cm)	84.75±9.36	85.52±7.57	85.06±8.11	86.70±6.78	0.818[1]
MUAC					0.781[3]
High	4 (50.0)	14 (60.9)	22 (64.7)	14 (70.0)	
WNL	4 (50.0)	9 (39.1)	12 (35.3)	6 (30.0)	
Neck circumference					0.597[2]
High	1 (12.5)	3 (13.0)	2 (5.9)	3 (15.0)	
WNL	7 (87.5)	20 (87.0)	32 (94.1)	17 (85.0)	
Waist circumference					0.941[2]
High	3 (37.5)	9 (39.1)	15 (44.1)	7 (35.0)	
WNL	5 (62.5)	14 (60.9)	19 (55.9)	13 (65.0)	
Serum free T3 (2.6-5.7pg/mL)	2.62±0.77	2.82±0.70	2.71±0.61	2.86±0.84	0.417[1]
Serum free T4 (9-19ng/dL)	0.93±0.39	1.01±0.41	0.94±0.38	0.98±0.49	0.893[1]
Serum TSH (0.35-4.94μIU/mL)	6.13±3.79	5.06±3.10	4.86±3.52	6.33±3.77	0.125[1]
Serum Free T3					0.709[3]
Low	3 (37.5)	5 (21.7)	12 (35.3)	6 (30.0)	
Normal	5 (62.5)	18 (78.3)	22 (64.7)	14 (70.0)	
Serum Free T4					0.545[3]
Low	3 (37.5)	5 (21.7)	7 (20.6)	7 (35.0)	
Normal	5 (62.5)	18 (78.3)	27 (79.4)	13 (65.0)	
Serum TSH					0.568[3]
High	3 (37.5)	6 (26.1)	8 (23.5)	8 (40.0)	
Normal	5 (62.5)	17 (73.9)	26 (76.5)	12 (60.0)	
Thyroid Status					0.534[2]
Euthyroid	4 (50.0)	17 (73.9)	22 (64.7)	12 (60.0)	
Subclinical hypothyroidism	1 (12.5)	0 (0.0)	4 (11.8)	1 (5.0)	
Overt hypothyroidism	3 (37.5)	6 (26.1)	8 (23.5)	7 (35.0)	
Hypothyroidism (Yes)	4 (50.0)	6 (26.1)	12 (35.3)	8 (40.0)	0.614[3]

***Significant at P<0.05, 1Kruskal–Wallis Test, 2Fisher's exact test, 3Chi-squared test, BMI: Body mass index, TSH: Thyroid-stimulating hormone, MUAC: Mid upper arm circumference

ratio was found to be 2.4:1 with mean age 60.82 (standard deviation 7.43). Among all patients, 68.2% (n=58) were smokers and 31.8% (n=27) were nonsmokers (Table 1; Figures 1 and 2).

The following variables were significantly associated (P<0.05) with the variable "GOLD Stage:" Weight (Kg), BMI, and obese (Table 2).

DISCUSSION

The study recruited 85 patients of COPD without any known pre-existing thyroid surgery. The male female ratio was found to be 2.4:1 with mean age 60.82 (SD 7.43).

Chaudhary et al.[15] in their study find similar results with mean age of the study population was 57.75±9.81 years

and no significant association is present between age and COPD stage. Age of patients ranged from 40 to 80 years.

In present study, 60 (70.6%) of the participants were male and 25 (29.4%) were females. As smoking is an important risk factor for COPD, and smoking is more common in males and that is why males have higher incidence of COPD. Some of females were exposed to biomass fuel smoke and that might be responsible for COPD. Similar result was found in the study done by Chaudhary et al.,[15] with male (73.7%) to female (26.3%) ratio as 2.8:1. Study done by Verma et al.[16] shows that among 121 patients, 90 were male and 31 were female with male predominance to male and female ratio of 2.9/1.

In this study, 30 (35.3%) COPD patient having abnormal thyroid profile and all 30 (35.3%) were diagnosed as hypothyroid. Out of total hypothyroid participants, 13.3% were in GOLD stage 1, 20% were in GOLD stage 2, 40% were in GOLD stage 3, and 26.7% were in GOLD stage 4.

Result more or less similar to our study, was found in the study conducted by Chaudhary et al.,[15] their study shows similar result and found that out of 171 patients, thyroid dysfunction was present in 43 patients. All of them were hypothyroid. The prevalence of thyroid dysfunction was 25%. In Stage A it was 8.6%, Stage B 22.7%, Stage C 32.5%, and in Stage D 32.7%. The prevalence of thyroid dysfunction was higher in higher stages of COPD as compared to that in the lower stages of COPD. This difference was statistically significant (P=0.047), but in our study, prevalence of thyroid disorder/hypothyroidism was not found to be significant in GOLD COPD stages.

The study done by Sebasan and Baliga,[17] among 50 COPD patients, 36% of patients had normal thyroid hormone levels, that is, Euthyroid, 54% had Overt Hypothyroidism, and 10% had ScH. In 36 patients with moderate COPD, 47.2% had overt hypothyroidism, and 8.3% had ScH. In 14 patients with moderate COPD, 71.4% had overt hypothyroidism, and 14.3% had ScH, shows prevalence of thyroid disorder that is Hypothyroidism more than found in our study.

Ragavan and Prabhu[18] was found that severity of COPD progress thyroidal biochemical of Overt and ScH was observed. From the study, it is found that COPD individuals progress in the airflow limitation from mild to moderate and then to severe COPD stages, they encounter hypothyroidism biochemical features of elevated TSH with lower values of FT3 and FT4 which remarkably affects the quality of life of COPD individuals.

Zewari et al.[19] studied 1654 COPD patients and found that obesity was significantly less common in GOLD Stage IV (10.1%) compared to GOLD I (20.5%), II (27.8%), and III (18.9%).

In study it was found that obesity is significantly associated ($P<0.05$) with, COPD GOLD stage and hypothyroidism. There was a significant difference between obesity in terms of distribution of GOLD Stage ($\chi^2=24.388$, $P\leq0.001$). 21.2% subjects were found to be obese. 38.9%, 27.8%, 22.2%, and 11.1% of the total obese belong to GOLD Stages 1, 2, 3, and 4, respectively.

Study by Yohannes and Perkins[20] found that the prevalence of obesity in COPD patients ranges from 10% to 25% which was similar to this study.

Sun et al.[21] performed meta-analysis of 5 randomized control trials involving BMI and COPD and in the study it is found that the estimated rate of FEV1 decline decreased with increasing BMI. Meta-regression of the estimates showed that BMI was significantly associated with the rate of FEV1 decline (linear trend $P=1.21\times10^{-5}$). The estimated rate of FEV1 decline decreased with increasing BMI. Meta –regression of the estimates showed that BMI was significantly associated with the rate of FEV1 decline (linear trend $P=1.21\times10^{-5}$). The novel finding supports the obesity paradox in COPD, compared to normal BMI. Low BMI is a risk factor for accelerated lung function decline, while high BMI has protective effect.

Limitations of the study

Hypothesis is not applicable, because it is hospital based study. The phenomenon of "obesity paradox" obesity and improved outcome in COPD is needed for further evaluation.

CONCLUSION

- Subjects found in our study having deranged thyroid profile were diagnosed as Hypothyroidism (both overt and ScH). But no significant association was found to be present between hypothyroidism and COPD GOLD stages
- The result of the study shows that thyroid disorder is quite frequent among COPD patients, and most of them have thyroid profile in lower range, and thus most of patients were having hypothyroidism. The study needs to further evaluated with more sample size
- In the study, it was found that underweight and normal weight were maximum in severe COPD stages that is COPD stage 3 and stage 4. And overweight and obese were maximum in COPD stages 1 and 2
- From the study, it was found that BMI of patient decreases with increase in GOLD COPD staging. This indicate that obesity might have some protective effect

in COPD but this needs to be further evaluated
- The mechanism responsible for the association of thyroid disorders with COPD is not yet fully understood but the systemic effects of inflammation in COPD have been suggested as the link.

ACKNOWLEDGMENTS

We are thankful to all participants for their support to this study, seniors for the guidance.

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Authors' Contributions:
DS- Definition of intellectual content, literature survey, prepared first draft of manuscript, implementation of study protocol, data collection, data analysis, manuscript preparation, and submission of article; **AC-** Design of study, statistical analysis and interpretation, review manuscript; **AKS-** Concept, design, clinical protocol, manuscript preparation, editing, and manuscript revision, literature survey; **AS-** Coordination and manuscript revision.

Work attributed to:
Department of Pulmonary Medicine, MLN Medical College, Prayagraj, Uttar Pradesh, India.

Orcid ID:
Dr. Anjuman Chaudhary - https://orcid.org/0000-0001-6350-6955

Source of Support: Nil, **Conflicts of Interest:** None declared.