Original article:

A study of risk factors for metabolic syndrome in chronic obstructive pulmonary disease patients

HAMZA A* , Meena R C , Gupta P R, Kumar P, Soothwal P, Sharma D, Khublani T K, Dubey V, Bedi M

Department of Respiratory Medicine, National Institute of Medical Sciences and Research, Jaipur
Corresponding author *

Abstract:

Aims and Objectives: To study the prevalence of Metabolic Syndrome (MET'S) in Chronic Obstructive Pulmonary Disease (COPD) and to find out different risk factors that contributes to Metabolic Syndrome in Chronic Obstructive Pulmonary Disease.

Material and Methods: An observational study done on all patients with clinical history consistent with Chronic Obstructive Pulmonary Disease and diagnosed so as per GOLD guidelines (GOLD-2016), during January 2017 to June 2018. Age & Sex matched healthy subjects formed the control group. The Test group and Control group was consisted of 260 subjects each. A detailed clinical history, physical examination and investigations were done. Met'S was diagnosed as per modified NCEPATP III criteria. The risk factors were studied in both the groups and to assess the contribution of risk factors in the development of Met'S.

Results: The Metabolic Syndrome was found to be more in COPD patients than in Control Group. Sedentary Life Style and Higher BMI significantly contributed to the development of Met'S in both Test and Control Group and other factors like Age, Sex, Smoking Index, type of Smoking & severity of COPD did not contribute.

Introduction

Chronic obstructive pulmonary disease (COPD) is a growing epidemic and remains a major public health problem.[1-3] The overall prevalence of COPD is estimated to be in the vicinity of 4-5% in our country.[4,5] An inappropriate/excessive inflammatory response of the lungs to respiratory pollutants, mainly tobacco smoking is hallmark of COPD. It is a complex and progressive disease and one of the main causes of morbidity and mortality worldwide. COPD is characterized not only by airway inflammation but also by systemic inflammation. The precise relationship between these two inflammatory processes is still unknown. Systemic inflammation is responsible for a significant amount of comorbidity in COPD patients.[6-8] Fabbri et al considered COPD as a part of the chronic systemic inflammatory syndrome.[9]

As a result, many of these patients have co-morbidities as well due to circulating inflammatory mediators. These include skeletal muscle wasting and cachexia, ischemic heart disease, heart failure, osteoporosis, normocytic anemia, diabetes, depression and metabolic syndrome.[10]Metabolic syndrome (Met'S) is a complex of interrelated medical disorders that increase the risk of developing an atherosclerotic cardiovascular disease and Type-2 Diabetes. These risk factors are abdominal obesity, elevated blood glucose, hypertension and dyslipidemia [elevated triglycerides and low levels of high-density lipoprotein (HDL) cholesterol] [11]. Metabolic syndrome is age dependent[12] and has been related to several other health conditions[13] and an increased mortality risk[14]. In addition, metabolic syndrome

www.ijbamr.com P ISSN: 2250-284X , E ISSN : 2250-2858

has clinically relevant negative effects on subjects exercise capacity[15], as well as on health status[16], while protective effects are described on bone mineral density (BMD) [17].

Metabolic-Syndrome (Met'S) is found to be twice more common in COPD when compared to the general population[18]. By 2016 it is estimated that about 59.1 lakh people in urban areas and 163 lakh people in rural areas in India will suffer from COPD.[18] The prevalence of obesity and metabolic syndrome is rapidly increasing in India and approximately about one-third of the urban populations have Met'S.[19]

Several workers have reported increased prevalence of Met'S in COPD. Lam et al [20], Akpinar et al[21], Wells CE et al [22], Lazovic et al[23], Breyer et al[24] ,Dave et al[10] , Naik D et al[25] ,M Lari S et al[26] ,Mekov E et al[27] ,Hazarika et al[28] ,Bulcun et al[29] and many more reported the increased prevelance of Met'S in COPD patients than in patients without COPD. Acharyya A et al in 2016[30] studied the association of Met'S and its components in COPD patients. They observed that the frequency of Met'S was highest when modified National Cholesterol Education Program-Third Adult Treatment Panel [modified NCEPATP III] was used as criterion as compared to rest but on multivariate analysis, a significant association of Met'S ($P<0.015$) with COPD was found only when the NCEPATP III criteria were used.

From the previous studies it was concluded that there is an inverse correlation of Met'S with severity of COPD based on GOLD criteria. This being so the inflammation theory behind Met'S is difficult to explain. None of the previous researchers have correlated the risk of Met'S (or its components) with severity of COPD based on risk factors. Further, obesity, by itself, is also associated with systemic inflammation and it is not very clear whether it is the associated obesity that causes the Met'S or the COPD itself.

AIMS & OBJECTIVES

- To study the prevalence of Metabolic Syndrome (Met'S) in Chronic Obstructive Pulmonary Disease (COPD)
- To find out different risk factors that contributes to Metabolic Syndrome (Met'S) in Chronic Obstructive Pulmonary Disease (COPD).

MATERIAL & METHODS

All outdoor & indoor patients attending the department of Respiratory Medicine at National Institute of Medical Sciences and Research, Jaipur with clinical history consistent with Chronic Obstructive Pulmonary Disease (COPD) and diagnosed so as per GOLD guidelines (GOLD-2016) [31], during January 2017 to June 2018.

Age & Sex matched healthy subjects formed the control group.

Approval of the Institutional Ethical Committee was obtained. A written informed consent was taken from all the patients after explaining the study protocol.

Type of Study: Observational Study.

Sample size was calculated in accordance to statistical methods. According to which the Test group and Control group was consisted of 260 subjects each. A p-value<0.05 were considered significant.

All the included subjects were evaluated as under:

1. A detailed clinical history and physical examination.
2. Peripheral Blood Tests: Complete Blood Counts, Urea, Creatinine, SGOT, SGPT, Fasting Blood Sugar, LDL cholesterol, HDL Cholesterol Level, Triglycerides & CRP.
3. Overnight and spot sputum sample for Acid Fast Bacilli by Ziehl-Neelsen method
4. Urine routine and microscopic examination
5. Chest roentgenograph (Postero-Anterior view).
6. Electrocardiography
7. Pre-bronchodilator Spirometry and post-bronchodilator Spirometry
8. Blood pressure
9. Anthropometric parameters including Waist circumference.
10. B.M.I

All Patients with Irreversible Airway Obstruction were recruited in the study subject to the their written consent & following inclusion and exclusion criteria:-

Inclusion Criteria:

1. Age between 20 to 80 years.
2. Body weight between 30 to 90 kg.
3. Willing to participate in study.

Exclusion Criteria:

1. Other illnesses like active pulmonary tuberculosis, Malignancy, Renal or Hepatic disease.
2. Present or past history of wheeze, chest tightness, eye allergy, nasal allergy or skin allergy, suggesting bronchial asthma.
3. H/O Acute Exacerbation of COPD or systemic steroid use in past 3 months.
4. Patients who refuse consent.

Met'S was diagnosed as per modified NCEP-ATP III criteria.[8]

Definitions of Metabolic Syndrome:

The modified NCEP criteria[32] require at least three of the following components:

1. Abdominal-Obesity (Waist Circumference ≥90 cm for Asian Men or ≥80 cm for Asian Women)
2. Triglycerides (TG) ≥ 150 mg/dL
3. HDL-Cholesterol ≤ 40 mg/dL for Men or 50 mg/dL for Women
4. Systolic/Diastolic Blood-Pressure ≥ 130/85 mmHg or receiving drug treatment.
5. Fasting Plasma Glucose ≥ 100 mg/dL.

www.ijbamr.com P ISSN: 2250-284X , E ISSN : 2250-2858

Severity Stage Characteristics of COPD (GOLD Criteria)

In Patients with $FEV_1/FVC<0.70$:		
Gold1	Mild	$FEV_1 > 80\%$ predicted
Gold2	Moderate	$50\% < FEV_1 < 80\%$ predicted
Gold3	Severe	$30\% < FEV_1 < 50\%$ predicted
Gold4	Very Severe	$FEV_1 < 30\%$ predicted

There are two methods of assessing the exacerbation risk. One is using the GOLD spirometric classification with GOLD 3 or 4 indicating high risk. The other is patient's history of exacerbations with two or more in the preceding year indicating high risk.[8] By using the above parameters, patients are classified into four groups.

Group A : low risk, less symptoms
Group B : low risk, more symptoms
Group C : high risk, less symptoms
Group D : high risk, more symptoms

Statistical analysis:

The data collected were analyzed for validity statistically with the software SPSS (Statistical Package for the Social Science.

RESULTS

This was an observational study done on patients with clinical history consistent with Chronic Obstructive Pulmonary Disease (COPD), diagnosed so as per GOLD guidelines (GOLD-2016) [33], during January 2017 to June 2018. Age and sex matched healthy subjects were taken as the control group. Met'S was diagnosed in all the subjects as per modified NCEPATP III criteria[49].

Maximum patients were 46 years or above. The mean age of the patients in test group was 59.78±12.85 years & 57.99±14.37 years in control subjects & the mean value of BMI in Test group was 24.78±3.23 kg/m^2 and in control group, 24.52±2.32kg/m^2. Statistically this difference was non-significant. (Table 1)

www.ijbamr.com P ISSN: 2250-284X , E ISSN : 2250-2858

Table 1-Distribution of Subjects according to :

	TEST	**CONTROL**	**P-VALUE**
AGE	59.78 + 12.85	57.99 + 14.37	0.1328
BMI	24.78+3.23	24.52+2.32	0.2923

Male preponderance (68.08% in case & 61.54% in control group) was evident in our study. In spite of best efforts, the male to female ratio was low in test group as compared to the control group but statistically the 2 groups were still similar.(Table 2)

Table 2: Distribution of Subjects According to Gender

Gender				
	Case		**Control**	
	Frequency	Percent	Frequency	Percent
F	83	31.92	100	38.46
M	177	68.08	160	61.54
Chi-test	2.159			
p value	0.0643			

Table 3 depicts the life style. In case & control group, 55% & 60.4% of the patients were non-sedentary. Sedentary life style was evident in 45% in case group & 39.62% in control group. Statistically non-significant in our study.

Table 3: Distribution of Subjects According to Life Style

Life style				
	Case		Control	
Non-Sedentary	143	55.00	157	60.38
Sedentary	117	45.00	103	39.62
Chi-test	1.332			
p value	0.2485			

Majority of cases were seen in 500-1000 smoking index (58.46%) followed by <500 smoking index (26.92%) and >1000 smoking index (14.62%). (Table 4)

www.ijbamr.com P ISSN: 2250-284X , E ISSN : 2250-2858

Table 4: Distribution of Subjects According to Smoking Index

Smoking Index		
<500	70	26.92%
500-1000	152	58.46%
>1000	38	14.62%

The majority of COPD cases were seen in GOLD criteria 2 & 3 (42.69% & 42.31%). (Table 5)

Table 5: Distribution of Subjects According to GOLD Criteria

Gold Criteria		
	Frequency	Percentage
1	11	4.23%
2	111	42.69%
3	110	42.31%
4	28	10.77%

According to ABCD criteria, the maximum of COPD cases were seen in D & A (46.92% & 33.08% respectively), followed by B (10.77%) & C (9.23%).(Table 6)

Table 6: Distribution of Subjects According to ABCD Criteria

ABCD Criteria		
	Frequency	Percentage
A	86	33.08%
B	28	10.77%
C	24	9.23%
D	122	46.92%

The positive metabolic syndrome in Test group was 26.15% & 9.62% in control group. (Table 7)
The prevalence of metabolic syndrome in COPD patients was 26.15% in our study.

Table 7: Distribution of Subjects According to Metabolic Syndrome

Met'S	**Test**	**Percentage (%)**	**Control**	**Percentage (%)**
Positive	68	26.15	25	9.62
Negative	192	73.85	235	90.38
Total	260	100.00	260	100.00

www.ijbamr.com P ISSN: 2250-284X , E ISSN : 2250-2858

Table 8: Correlation of COPD With Met'S

Correlation	95% CI	P-value
Age	0.018	0.886
Sex	0.5386	0.5216
Life style	0.04295	<0.0001***
BMI	-0.088	<0.0001***
Smoking index	0.987	0.104
GOLD criteria	0.887	0.113
ABCD criteria	0.952	0.058

The above table depicts the correlation of Met'S with various parameters in the test group. While age, gender, smoking index, and severity of COPD did not correlate with Met'S, Life style & BMI of the COPD patients was highly correlated to the occurrence of Met'S i.e. Patients with high BMI and sedentary life style were more prone to metabolic syndrome in our study.

DISCUSSION

This observational study was conducted to find out the prevalence of Metabolic Syndrome (Met'S) and associated risk factors in stable patients of Chronic Obstructive Pulmonary Disease (COPD). Age & Sex matched non-smoker healthy subjects were taken as control.Males predominated in the study group. The Male predominance in COPD patients is well established.[34] Similarly COPD was more common in patients above 45 years of age. The older age predominance in COPD is well established. Since the controls were Age & Sex matched, there was no difference in Age & Sex of the Test & Control group patients. So the study data are valid for comparison on this account.

The mean BMI in Test Group was 24.78 and in Control Group was 24.52 and the difference between the two was Non-significant (p-value: 0.2923). More patients in Test Group were Sedentary as compared to Control Group (117/103). Still the difference was statistically Non-significant. Since Age, Sex, BMI, Lifestyle were similar in Test & Control Group patients of our study, the study data were comparable for statistical validity.

Although the two groups were statistically comparable yet Met'S was more common in COPD patients (68/260) as compared to Controls (25/260). Thus Met'S is clearly more common in COPD Patients as compared to healthy non-smoker controls. This is in line with the observations made in earlier studies[20, 22,24,35], although the prevalence of Met'S varied from 20% to 57%. [20,24] The difference in prevalence of Met'S in different studies could be related to Geographical differences, Socio-Economical status and other parameters related to COPD patients.

We also correlated various parameters that could contribute to Met'S in COPD patients. In our study, Age, Sex, Smoking-Index, Gold Staging & ABCD categories were unrelated to Met'S in COPD. But Sedentary Lifestyle & higher BMI were Significantly correlated to the prevalence of Met'S in these COPD patients (p-value: <0.0001). Robert Eckel et al[12] reported that the Met'S is a common metabolic disorder that results from the increasing prevalence of obesity and it has advantages in terms of risk communication, particularly in young people.Akpinar EE et al[21] reported that the frequency of

www.ijbamr.com P ISSN: 2250-284X , E ISSN : 2250-2858

metabolic syndrome was higher in patient group than control subjects. Abdominal obesity, hypertension, hyperglycemia components of metabolic syndrome were significantly more prevalent in patient group.

Well CE et al[22] reported People with COPD have multiple risk factors predisposing to Met'S and Diabetes. They have an increased risk of obesity, tend to be sedentary, have increased inflammation and oxidative stress and are treated with corticosteroids. Diabetes Mellitus and Met'S are around 1.5-times more common in people with COPD than in the general population.

Breyer MK et al[24] reported that Met'S is more prevalent in overweight or obese COPD patients than in BMI matched healthy subjects. In contrast to our study Lazovic B et al[23], reported Met'S was more common in females than in males. M Lari S et al[26] reported that the frequency of Met'S was found to be more common in mild to moderate stages of COPD. Bulcun E et al[29] reported that the rate of Met'S in patients with stage II COPD was higher than the patients with stage IV COPD. From the above discussion and results of our study, it can be safely concluded that Met'S in COPD is more related to sedentary Lifestyle & higher BMI, rather than COPD by itself. Breyer M K et al [24] have also reported similarly.

CONCLUSION

Metabolic-Syndrome (Met'S) is a complex of interrelated medical disorders that increase the risks of developing an atherosclerotic cardiovascular disease and Type-2 Diabetes. Review of literature revealed that it's more common in Chronic Obstructive Pulmonary Disease (COPD) than in general population but there is also an inverse correlation of Met-S with severity of COPD. This being so, the inflammation theory behind Met-S is difficult to explain. None of the previous researchers have correlated the risk of Met'S (or its components) with severity of COPD based on risk factors. Further, obesity, by itself, is also associated with systemic inflammation. Therefore, it is not very clear whether the increased prevalence of Met-S is due to COPD or the associated obesity. It was therefore hypothesized that Chronic Obstructive Pulmonary Disease (COPD) by itself may or may not contribute to Metabolic Syndrome (Met'S) and a study was undertaken at National Institute of Medical Sciences & Research, Jaipur with the following aims and objectives:-

1. To study the prevalence of Metabolic Syndrome (Met'S) in Chronic Obstructive Pulmonary Disease (COPD) and
2. To find out different risk factors that contributes to Metabolic Syndrome (Met'S) in Chronic Obstructive Pulmonary Disease (COPD).

The results of the study were as under:-

1. Male outnumbered females in both the case and control group (68.08% and 61.54% respectively). The mean age of the patients in test group was 59.78±12.85 years as compared to 57.99±14.37 years in control subjects.
2. Mean BMI in case group was 24.78±3.23 $kg/m^2$and as compared to 24.52±2.32kg/m^2 in controls.
3. A sedentary life style was evident in 45% & 39.62% of the case and control subjects.
4. Majority of COPD patients fell in smoking index of 500-1000 (58.46%).

5. Majority of COPD cases qualified for GOLD criteria of 2 & 3 (42.69% & 42.31% respectively). Majority of them qualified for category D (46.92%).
6. Metabolic syndrome (Met'S) was positive in 26.15% & 9.62% of the case and control group subjects respectively.
7. Age, gender, smoking index, and severity of COPD did not correlate with Met'S but sedentary life style & high BMI in COPD patients was highly correlated to the occurrence of Met'S in them.

From the above results of this study, it can be concluded that Met'S is more common in COPD patients as compared to age and sex matched controls and sedentary life style & high BMI are the major risk factors that contribute to Met'S in COPD. Age, gender, smoking index, and severity of COPD did not correlate to occurrence of Met'S in COPD patients. Whether sedentary life style & high BMI solely contribute to Met'S in these patients is difficult to say as Mean BMI was similar in case and control group subjects and sedentary life style was only marginally higher in case group as compared to controls. Larger studies are required to further substantiate the results of the current study.

LIST OF ABBREVIATIONS

BMI	:	Body mass index
CI	:	Confidence Interval
COPD	:	Chronic obstructive pulmonary disease
CXR	:	Chest X-ray
CAD	:	Coronary Artery Disease
CVD	:	Cardio Vascular Disease
CHD	:	Coronary Heart Disease
ECG	:	Electrocardiogram
FBS	:	Fasting Blood Sugar
FEV_1	:	Forced expiratory volume in 1 second
FEV_1/FVC	:	Forced expiratory volume in 1 second/Forced vital capacity
FFA		Free Fatty Acids
GOLD	:	Global Initiative for Chronic Obstructive Lung Disease
HDL	:	High Density Lipoprotein
HS-CRP	:	High Sensitivity C-Reactive Protein
IDF	:	International Diabetes Federation
LDL	:	Low Density Lipoprotein
MET'S / MS	:	Metabolic Syndrome
mMRC	:	Modified Medical Research council
NCEP-ATP-III	:	National Cholesterol Education Program-Adult Treatment Panel-3

www.ijbamr.com P ISSN: 2250-284X , E ISSN : 2250-2858

PFT	:	Pulmonary Function Test
SPSS	:	Statistical Package For the Social Sciences
SD	:	Standard Deviation
SGOT/PT	:	Serum Glutamic Oxaloacetic Transaminase/ Pyruvic transaminase
SPO_2	:	Saturation Pulse oxygen
Sputum AFB	:	Sputum for Acid Fast Bacilli
T2DM	:	Type 2 Diabetes Mellitus
TG	:	Triglycerides
VLDL	:	Very Low Density Lipoprotein
WHO	:	World Health Organization

REFRENCES

1. Lopez AD, Shibuya K, Rao C, Mathers CD, Hansell AL, Held LS, et al. Chronic obstructive pulmonary disease: Current burden and future projections. Eur Respir J. 2006;27:397–412.
2. Halbert RJ, Natoli JL, Gano A, Badamgarav E, Buist AS, Mannino DM. Global burden of COPD: Systematic review and meta-analysis. Eur Respir J. 2006;28:523–32.
3. Fukuchi Y, Nishimura M, Ichinose M, Adachi M, Nagai A, Kuriyama T, et al. COPD in Japan: The Nippon COPD Epidemiology study. Respirology. 2004;9:458–65.
4. Jindal SK, Aggarwal AN, Chaudhry K, Chhabra SK, D' Souza GA, Gupta D, et al. A multicentric study on epidemiology of chronic obstructive pulmonary disease and its relationship with tobacco smoking and environmental tobacco smoke exposure. Indian J Chest Dis Allied Sci. 2006;48:23–9.
5. McKay AJ, Mahesh PA, Fordham JZ, Majeed A. Prevalence of COPD in India: A systematic review. Prim Care Respir J. 2012;21:313–21.
6. Rabe KF, Wedzicha JA, Wouters EFM. Introduction. Rabe KF, Wedzicha JA, Wouters EFM (eds). COPD and Comorbidity. European Respiratory Society, Sheffield. 2013:ix–x.
7. Agusti A, Soriano JB. COPD as a systemic disease. COPD. 2008;5:133–138.
8. Barnes PJ. Chronic obstructive pulmonary disease: effects beyond the lungs. PLoS Med. 2010;7:e1000220.
9. Fabbri LM, Rabe KF. From COPD to chronic systemic inflammatory syndrome? Lancet. 2007;370:797–799.
10. DaveL, GardeS, AnsariOA, ShrivastavaN, SharmaVK. COPD, Metabolic syndrome. A study of association between metabolic syndrome and copd.2014 Feb 6(4294).
11. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. International Diabetes Federation Task Force on Epidemiology and Prevention; Hational Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the Study of Obesity. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120:1640–1645.
12. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet,2005; 365: 1415–1428.

13. Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care,2001; 24: 683–689.
14. Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. Jama,2002; 288: 2709–2716.
15. Ribisl PM, Lang W, Jaramillo SA, Jakicic JM, Stewart KJ, et al. (2007) Exercise capacity and cardiovascular/metabolic characteristics of overweight and obese individuals with type 2 diabetes: the Look AHEAD clinical trial. Diabetes Care 30: 2679–2684.
16. Ford ES, Li C .Physical activity or fitness and the metabolic syndrome. Expert Rev Cardiovasc Ther,2006; 4: 897–915.
17. Kinjo M, Setoguchi S, Solomon DH. Bone mineral density in adults with the metabolic syndrome: analysis in a population-based U.S. sample. J Clin Endocrinol Metab,2007; 92: 4161–4164.
18. Murthy KJ, Sastry JG. NCMH Background Papers-Burden of Disease in India. New Delhi, India: 2005. Sep, Economic burden of chronic obstructive pulmonary disease; pp. 263–74.
19. Misra A, Chowbey P, Makkar BM, Vikram NK, Wasir JS, Chadha D, et al. Consensus statement for diagnosis of obesity, abdominal obesity and the metabolic syndrome for Asian Indians and recommendations for physical activity, medical and surgical management. J Assoc Physicians India. 2009;57:163–70.
20. Lam KB, Jordan RE, Jiang CQ, Thomas GN, Miller MR, Zhang WS, et al. Airflow obstruction and metabolic syndrome: The Guangzhou Biobank Cohort Study. Eur Respir J. 2010;35:317
21. Akpinar EE, Akpinar S, Ertek S, Sayin E, Gulhan M. Systemic inflammation and metabolic syndrome in stable COPD patients. Tuberk Toraks. 2012;60(3):230-7.
22. Wells CE, Baker EH. Metabolic syndrome and. European Respiratory Monograph 59: COPD and Comorbidity. 2013Mar1;59:117.
23. Lazovic B, Stajic Z, Mazic S, Đelić M. Prevalence of metabolic syndrome in patients suffered from chronic obstructive pulmonary disease. Sadržaj.:229.
24. Breyer MK, Spruit MA, Hanson CK, Franssen FM, Vanfleteren LE, Groenen MT, Bruijnzeel PL, Wouters EF, Rutten EP. Prevalence of metabolic syndrome in COPD patients and its consequences. Plo Sone. 2014 Jun20 ;9(6):e98013.
25. Naik D, Joshi A, Paul TV, Thomas N. Chronic obstructive pulmonary disease and the metabolic syndrome: Consequences of a dual threat. Indian journal of endocrinology and metabolism. 2014 Sep1;18(5):608.
26. MLari S, Attaran D, Rokni Yazdi H, Towhidi M, Shadkam O, Asadi A, Khajehdaluee M, Ayatollahi H, Ghayour-Mobarhan M. Metabolic Syndrome in Chemical Warfare Patients with COPD. Journal of Cardio-Thoracic Medicine. 2014;2(4):231-7.
27. Mekov E, Slavova Y, Tsakova A, Genova M, Kostadinov D, Minchev D, Marinova D. Metabolic syndrome in hospitalized patients with chronic obstructive pulmonary disease. Peer J. 2015Jul 2 ;3:e1068.
28. Hazarika B, Raghavendra MK, Choudhary S, Basumotary N, Sarmah K, Sharma J. Late-Breaking Abstract: Prevalence of metabolic syndrome in COPD and its association with severity of disease. European Respiratory Journal. 2015 Sep 1;46(suppl59):PA677.
29. Bulcun E, Ekici A, Ekici M. Metabolic Syndrome And Chronic Diseases In Patients With Chronic Obstructive Pulmonary Disease.

30. Acharyya A, Shahjahan MD, Mesbah FB, Dey SK, Ali L. Association of metabolic syndrome with chronic obstructive pulmonary disease in an Indian population. Lung India: Official Organ of Indian Chest Society. 2016 Jul;33(4):385.
31. Global Strategy For The Diagnosis, Management, And Prevention Of chronic Obstructive Pulmonary Disease updated 2016. at:http://www.goldcopd.org/ guidelines global strategy- for-diagnosis-management. Html accessed on 23rd Nov, 2016.
32. S.M. Grundy, J. I. Cleeman, S. R. Daniels et al., "Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement," Circulation,2005; vol. 112, no. 17, pp. 2735–2752.
33. McDonough JE, Yuan R, Suzuki M, et al. Small-airway obstruction and emphysema in chronic obstructive pulmonary disease. N Engl J Med 2011; 365:1567.
34. Terzikhan N, Verhamme KMC, Hofman A, Stricker BH, Brusselle GG, Lahousse L. Prevalence and incidence of COPD in smokers and non-smokers: the Rotterdam Study. *European Journal of Epidemiology*. 2016;31(8):785-792. doi:10.1007/s10654-016-0132-z.
35. Marquis K, Maltais F, Duguay V, Bezeau AM, LeBlanc P, Jobin J, *et al.* The metabolic syndrome in patients with chronic obstructive pulmonary disease. J Cardiopulm Rehabil 2005;25:226-32.