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Original Research Article

SPIROMETRIC INDICES IN PATIENTS OF COPD ASSOCIATED DIABETES IN RURAL CENTRAL INDIA- A CASE-CONTROL STUDY.

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Abstract

BACKGROUND: Every complication arising among diabetic patients is secondary to vascular damage thereby affecting the blood supply and leading to ischemic tissue injury.

AIM: To determine the difference in Pulmonary Function Tests parameters among diabetic and non-diabetic COPD patients.

MATERIAL AND METHODS: This was a hospital-based case-control observational study. We included 103 (50 cases & 53 controls) patients who were diagnosed with COPD and aged more than 40 years. Cases were diabetic patients and controls were nondiabetic patients (based on HB1AC). The PFT was measured by Helios Spirometer subjected to post-bronchodilator spirometry evaluation of FEV_1, FVC, and FEV_1/FVC.

RESULTS: The mean FEV1 among the cases and control was 38.60 and 59.54, respectively, p= 0.0001. The mean FVC among cases was 64.46 and among controls was 72.15 (p-value = 0.0001). The mean Peak Expiratory Flow Rate among cases was 191.54 and the control was 257.39 (P-value = 0.0001). The mean FEV1/FVC ratio among cases was 0.59 and controls was 0.64 (P-value = 0.0001). There was a strong but negative correlation between FEV1 and HbA1C (r = -0.866; P-value =0.0001).

CONCLUSION: PFT values were significantly lower among diabetic patients in comparison to non-diabetic COPD patients. Moreover, there was a strong and inverse relation between PFT and HbA1C.

Keywords: COPD, Diabetes, Spirometry, HB1AC, FEV_1

INTRODUCTION:

"Chronic Obstructive Pulmonary Disease (COPD) is a common disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gas (1). The most common risk factor for the development of COPD is smoking (tobacco or

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marijuana) in form of cigars, pipes, cigarettes, bong, and water pipes which leads to accelerated age-related decline in lung function in form of forced expiratory volume in 1 second (FEV_1)(2). Non-smokers may also develop COPD as a long-term effect of exposure to noxious particles and gases which are also associated with a variety of host factors including airway hyper-responsiveness, genetics and poor lung growth in childhood(3). It has been estimated that COPD to become the fourth leading cause of death worldwide by the year 2030(4). Studies suggest that there is a prevalence of DM is common in COPD patients & prevalence varies between 2-37%(4). In DM, hyperglycaemia affects the respiratory system through oxidative stress, hypoxemia, systemic inflammation and changes in the structure of lung tissue that leads to altered gas exchange(5). DM leads to biochemical changes in the connective tissue of the lung particularly collagen and elastin and microangiopathy due to non-enzymatic glycosylation of proteins and extracellular proteins of lung parenchyma along with thickening of the basal lamina and increased susceptibility to infection with skeletal muscle weakness(5).

DM prevalence is rapidly growing worldwide and is estimated that there are 285 million people with DM worldwide. Most of the patients with DM are from developing countries. Data suggests that there are the top ten countries in the south Asia region (India, Bangladesh and Pakistan)in terms of the absolute number of DM patients(6).

The primary objective of this study was to examine the correlation between Diabetes Mellitus and pulmonary function in COPD patients in rural India.

MATERIAL AND METHODS:

The study was initiated after clearance from the institutional ethics committee, DMIMS (DU), Sawang (M), and Wardha. This study was an observational case-control study conducted at Acharya Vinobha Bhave Rural Hospital, Sawangi (Meghe) in indoor patients. The total duration of the study was 18 months. We included 103 patients who were admitted to the department of Respiratory Medicine and were diagnosed with COPD according to GOLD's guidelines. We included patients aged more than 40 years. Cases were defined as "having both COPD and Diabetes. Controls were defined as COPD patients without diabetes mellitus. There was a total of fifty cases and 53 controls. We collected the data for the profile of the patients including age, gender, body mass index (BMI), GOLD staging, symptoms, signs, and history of exposure to risk factors like smoking and biomass fuel exposure. All the patients were subjected to Chest X-ray PA view and spirometry and relevant blood investigations for diabetes mellitus. COPD diagnosis was made based on history and spirometry. All the patients were subjected to Spirometry and PFT was performed by RMS Helios Spirometer were subjected to pulmonary function test using post-bronchodilator spirometry evaluation of Forced expiratory volume in one second (FEV1), Forced vital capacity (FVC), Ratio of FEV1/FVC, Peak Expiratory Flow Rate (PEFR)(1).

All the patients were subjected to HbA1c for the screening of DM. The cut-off point for the diagnosis of DM was 6.5 %. Patients whose HbA1c comes to be ≥6.5 % were considered diabetic, and those who were ≤ 6.5 % considered non-diabetic (7).

RESULTS:

Table 1 shows the socio-demographic profile of the cases and controls. The total n=50 cases (mean age 57.62) & n=53 controls (mean age 60.35) were included in study. Total number of males in cases are n=40 (80%) and females n= 10(20%). Total number of males in

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controls are n=39 (73.58%) and females n=14(26.42%). There are total of n=19 (38%) cases who were overweight i.e. {BMI 25-25.9}, n=22 (44%) cases, and n=12 (22.6%) controls, who had normal BMI i.e. {BMI 18.5-22.99}, and total of n=9 (18%) cases and n=41 (77.4%) controls whose BMI was <18.5 i.e., underweight. There were no patients in our study who comes under the GOLD-1 stage. There were 1 (2%) patients as cases and 48 (9.57%) patients as controls who fall under the GOLD-2 stage. There was a total of 45(90%) patients as cases and 5(9.43%) patients as controls, who come under the GOLD-3 stage and a total of 4(8%) cases who got admitted under the GOLD -4 stage. No patients got admitted under GOLD-4 as controls. There was a total of sixteen patients out of which 11 (22%) patients as cases and 5(9.43%) patients as controls who came with a previous history of pulmonary tuberculosis.

Table 1: Socio-demographic characteristics among participants (n=103)

	CASE	CONTROLS	p-Value
Age	57.6	60.3	0.13
Old Pulmonary TB	11(22%)	5(9.43%)	p-0.078
Smoking	36(72%)	26(49.06%)	p-0.017
Biomass Exposure	9(18%)	15(28.30%)	p-0.21
Hypertension	18(36%)	19(35.85%)	p-0.98
Anaemia	33(66%)	31(58.49%)	p-0.32
Gender			
Male	40 (80%)	39 (73.58%)	0.44
Female	10 (20%)	n = 14 (26.42%)	
BMI			
Underweight	9(18%)	41(77.4%)	p-0.0001
Normal	22(44%)	12(22.6%)	
Overweight	19(38%)	0 (0%)	
GOLD Staging			
Gold-1	0(0%)	0(0%)	p-0.0001
Gold-2	1(2%)	48(90.57%)	
Gold-3	45(90%)	5(9.43%)	
Gold-4	4(8%)	0(0%)	
Grade			
Grade-0	0(0%)	0(0%)	p-0.62
Grade-1	1(2%)	4(7.55%)	
Grade-2	16(32%)	15(28.30%)	
Grade-3	19(38%)	20(37.74%)	
Grade-4	14(28%)	14(26.42%)	
SPO2			
Normal	28(56%)	26(49.06%)	p=0.48
Decreased	22(44%)	27(50.94%)	

There was a total of sixty-two patients of which 36 (72%) cases and 26(49.06%) controls were previously smokers. Total of 9 (18%) patients as cases and 15(28.30%) patients as controls who have a previous history of biomass exposure. A total of 18 (36%) patients as cases and 19(35.85%) patients as controls were hypertensive. Only 1 (2%) patient a case, and 4(7.55%) patients as controls who falls under MMRC Grade-1 stage, 16(32%) case and

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15(28.30%) controls come under MMRC Grade-2 stage, 19(38%) case and 20(37.74%) controls, falls under MMRC Grade-3 stage, and 14(28%) case and 14(26.42%) controls, who come under MMRC Grade-4 stage. A total of 28 (56%) cases and 26(49.06%) controls had normal oxygen saturation & total of 22(44%) cases and 27(50.94%) controls had decreased oxygen saturation.

Table 2: Comparison of HbA1C, FBS/PMBS of cases and controls.

	Cases (n=50) (Mean ± SD)	Controls (Mean ± SD) (n=53)	p-value
HbA1C	(8.12 ±1.28)	(5.83 ±0.36)	0.0006
Fasting blood glucose (FBS)	169.78(±29.34)	105.13(±9.14)	0.008
Post-meal blood glucose (PMBS)	213.42(±38.32)	125.77(±15.45)	<0.0001

The mean HbA1C of the cases is 8.12 and of the controls is 5.83 (p =0.006) (Table 2). The mean FBS of the cases are 169.78 (± 29.34), and the mean FBS of the controls was 105.13 (± 9.14) which was statistically significant.

Table 3: Comparison of PFT among cases and controls (n=103)

PFT	Cases (n=50)	Controls (n=53)	P-value
FEV1	38.60 (±5.68)	59.54(±5.35)	0.0012
FVC	64.46 (±5.65)	72.15(±4.60)	<0.0001
FEV1/FVC	0.59 (±0.040)	0.64 (±0.045)	0.0001
PEFR	191.54 (±30.11)	257.39 (±53.79)	0.0001

The mean FEV1 among cases are 38.60 and the mean FEV1 among controls was 59.54 (p =0.0012). The mean FVC among cases and control was 64.46 and 72.15 (p < 0.0001). The mean Peak Expiratory Flow Rate (PEFR) of the cases are 191.54 and the control was 257.39. The mean FEV1/FVC ratio of the cases is 0.59 and the controls were 0.64 (p-value =0.0001).

Table 4: Correlation between HbA1C and FEV1 and FVC Pearson's Correlation Coefficient.

	Mean	Std. Deviation	N	R-value	p-value
HbA1C	7.01	1.35	103		
FEV1	49.37	11.86	103	-0.866	0.0001
FVC	68.41	6.41	103	-0.575	0.0001

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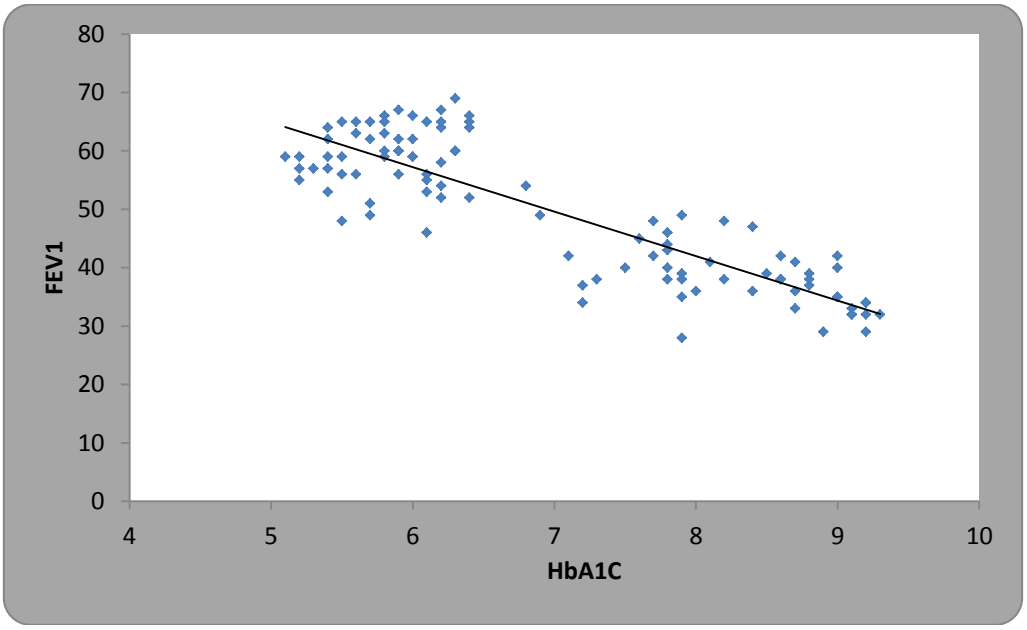

Figure-1.1: Correlation between HbA1C and FEV1

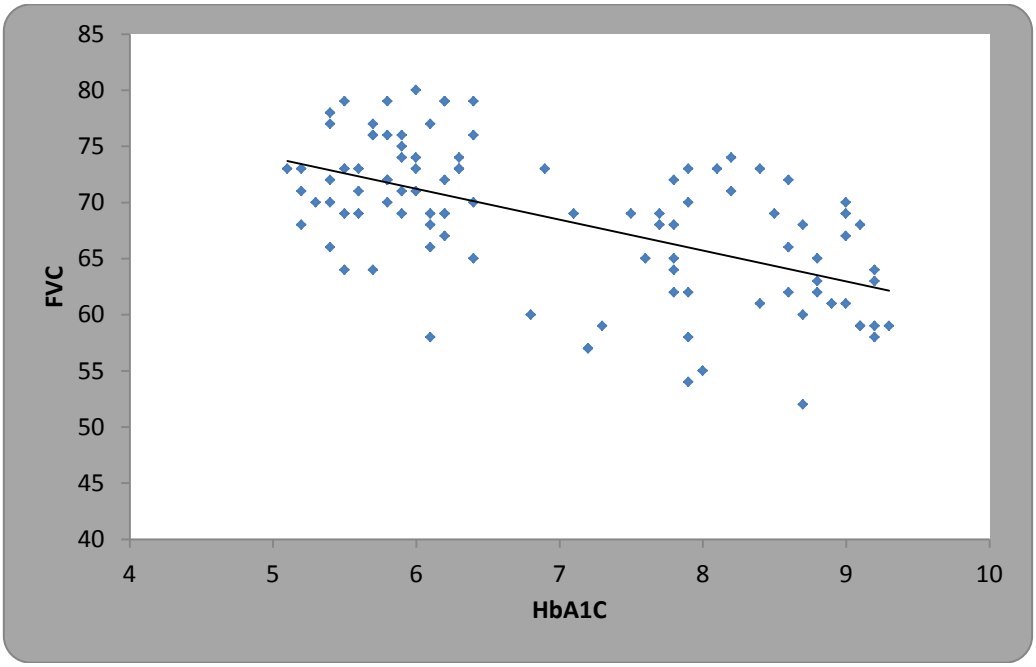

Figure-1.2: Correlation between HbA1C and FVC

Figure (1.1 &1.2) shows the correlation between HbA1C in all the patients included in the present study with FEV1 and FVC. In our study, we found that FEV1 shows a negative correlation with HbA1C, with a correlation coefficient (R-value) of -0.866 (P value = 0.0001). In present study FVC also shows negative correlation with HbA1C, (r = -0.575; P-value = 0.0001).

DISCUSSION

There are multiple studies conducted which show the correlation between DM type 2 in COPD patients. Multiple research projects have been conducted which show a positive correlation between the significant decrease in pulmonary function as FEV1, FVC,

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FEV1/FVC ratio, and PEFR in COPD patients with DM type 2. The patient's age ranges between 40 to 70 years with the mean age of the cases being 57.62 years and that of controls was 60.35±7.98 years. 29 (58%) of cases & 41 (77.36%) of control belonged to 51-70 years shows that COPD is a disease that affects old age people with male predominance as the total number of males was 40(80%) and females were 10(20%) as cases, and in controls, there was a total of 39(73.58%) males and 14(26.42%) females. Adiody et al. studied the impact of DM on PFT in COPD patients, which shows a maximum number of patients were in the age group 61-70 years group (5). Similar findings were reported by Mishra et al. who studied PFT in DM in COPD and found the mean age of the COPD with DM was 61.4(8), they also found male predominance in their study as they found the total number of males was 29(64.4%) as compared to females 16(35.6%) (8). Baker et al. also showed male predominance in the study as the total number of patients in the study was n=75 out of which 43 were males and 27 were females. (9).

All patients were categorized into four categories based on BMI of which 19(38%) cases were overweight, a total of 22(44%) cases and 12(22.6%) controls were within normal BMI & 9(18%) cases and 44(77.4%) controls were underweight. A study conducted by Baba et al. showed that the mean BMI of total patients in their study were found to be 23.2(±3.3). (10) All patients underwent PFT of which FEV1 was decreased in cases than in controls with the mean FEV1 of cases being 38.60%, and the mean FEV1 of controls was 59.54%. Mishra et al in 2012 also shows reduced FEV1 in DM-COPD as compared with COPD with asthma which was statistically significant(8). Davis et al also found that there is a significant decrease in FEV1 in patients with DMCOPD as a result of the glycosylation of proteins such as collagen in the chest wall and pulmonary tree (11). Adiody et al. in their study showed a significant decrease in FEV1 in DMCOPD patients as compared to COPD alone(5). Asanuma et al. found that FEV1 was decreased in male DM cases (116±13) as compared to non-DM controls(104±14)(12). COPD patients with DM have increased severity of airflow due to pulmonary microangiopathy thickening alveolar and capillary walls. In DM patients, pulmonary impairment is caused by four primary sources non-enzymatic glycosylation of lung collagen and elastin by advanced glycosylation end products (AGES) generated by disrupted glycaemic control resulting in reduced elasticity of the lung and thus reduces the lung function.

All the patients underwent PFT in which the FVC & FEV1/FVC ratio was found to be significantly decreased in cases than in controls with the mean FVC of the cases being 64.46, and of controls 72.15. Similar findings were reported by Kalappan et al. who found a decrease in FVC in DM (76.33±14.78) patients as compared to healthy controls(83.1±7.81), they also found FEV1/FVC ratio was decreased in DM type 2 patients age more than 35 years)(13). Mishra et al. in their study also found that there is a decrease in FVC in DM COPD as compared with COPD with asthma which was statistically significant(8). Asanuma et al. also found that FVC is decreased in DM preferably in males as compared to females(12). Adiody et al. in their study also found that post-bronchodilator FVC was further reduced in males than in females with COPD along with pre-existing DM, they also found a significant decrease in FEV1/FVC ratio in the patients with DM with COPD as compared to DM group(5). Decrease in FVC and FEV1/FVC ratio occurs due to non-enzymatic glycosylation that results in the alteration of connective tissue of the lung.

In our study, we found that the PEFR of the cases were decreased as compared to controls which come to be statistically Significant. Shah et al. also found that PEFR has decreased in

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DM type 2 patients as compared with non-diabetic(14). Andrew et al. in their study also found that PEFR has decreased in patients with DM type 2 patients(15). Kalappan et al. also found decreased PEFR in DM type 2 patients(13). Meo et al. also found a decrease in PEFR in patients of DM which was statistically significant with a P value of 0.001(16). In our study, we found a decrease in PEFR in patients of COPD with DM type-2 because of non-enzymatic glycosylation of lung collagen and elastin by advanced glycosylation end products.

All the cases and controls were subjected to blood investigations for HbA1c, FBS and PMBS and found that the values are much increased in COPD patients with DM type 2 which was statistically significant with a P value of 0.001 (<0.05). Similar findings were found in another study done by Rn and As in which they also found a negative correlation between HbA1C with FEV1 (r=-0.025) and FVC (r=-0.070) which was statistically significant(17). Kabeya et al. in 2014 found that HbA1C was negative correlated with FEV1 and FVC which was statistically significant (P<0.05).(18).Shah et al. in their study did not find any significant correlation between HbA1C with FEV1 and FVC (P>0.05).(14). FEV1 and FVC are significantly reduced in DM patients that results in restrictive lung pathology due to glycosylation of collagen, microangiopathy and systemic inflammation of respiratory muscles leads to restrictive lung function. In our study, mean HbA1C was found to be much higher in cases than compared to controls. Mean HbA1c in cases was found to be 8.12 as compared to controls which were 5.83. In our study, we also find a negative correlation between HbA1C with FEV1 (r=-0.866) and FVC (r=-0.575), which was statistically significant with a P value of 0.0001(<0.05).

We also found that most of the cases fall in the GOLD stage 3 (90%) - stage 4(8%), Whereas most of the controls fall in GOLD stage 2 (90.57%) – stage 3(9.43%). Kinney et al. in their study found that pulmonary function was found to be much decreased in patients with DM type 2 and they fall in severe stage 3 according to COPD guidelines which were statistically significant with a P value of 0.0001 (17). Mekov et al. in their study also found that DM patients with COPD fall in severe stages according to GOLD guidelines (4). Worsening of lung function in DM type 2 amongst COPD patients is supposed to be due to non-enzymatic glycosylation of elastin and collagen that reduced the lung elasticity and lung recoil because of advanced glycosylation end products.

Our study did not find any significant difference in lung function between DM patients with COPD to any previous history of pulmonary tuberculosis. A study conducted by Chung et al. found that after the completion of anti-tubercular treatment, DM patients developed obstructive lung disease more frequently(19). Another study conducted by Lee et al. found that patients with a previous history of pulmonary tuberculosis had altered lung function (20). In the study by Mohan et al (2007), a history of pulmonary TB was present in 28.4% of cases presented with AE-COPD(21). Pulmonary tuberculosis is related to the development of obstructive lung disease and patients with a previous history of TB are more likely to present with acute exacerbation.

In our study, we also found that a total of sixty-two patients out of 103 were smokers. Amongst them 36(72%) as cases and 26(49.06%) controls were present. We found that the effect of smoking in pre-existing DM type 2 patients of COPD had more decline in pulmonary function as compared to non-diabetic smokers. Manji et al. in their study also found that patients who are long-standing smokers had significantly higher chances to develop obstructive abnormalities. (22). Kinney et al. also found that the prevalence of

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smokers was higher in the COPD with DM group which results in a further decrease in lung function. Inhaled smoke in form of a bidi or cigarette causes acute changes in the lung and causes injury leading to resistance to airflow, cough, and irritation in the upper airway. We also found that lung function is further reduced in association with biomass exposure in cases than in controls, especially in females. Johnson et al. in their study found that women ≥ 50 years of age are more prone to develop COPD.(23). Behera and Jindal in their study also found a significant decrease in FEV1, FVC, and PEFR in Indian women who are exposed to biomass fuel(24). The use of biomass fuel for cooking in a rural area, in a closed kitchen is more likely related to develop COPD in Indian females, due to the close environment, emission of smoke and fumes results in higher levels of carboxy haemoglobin which in turn results in a decrease in oxygen carrying capacity of the blood, which cause dyspnea, and muscle fatigue.

Our study also found hypertension as a comorbid disease which is almost equal in both cases and controls which is not significant. Mannino et al. in a study show COPD with DM are associated with a higher risk of developing hypertension (25). The reason behind the association between hypertension and COPD seems to be related to systemic inflammation due to higher level of fibrinogen, chronic infections and other risk factors like smoking, biomass fuel exposure etc. It is also found that COPD patients with respiratory impairment were more likely to develop DM and hypertension and are at higher risk of hospitalization.

In 18 (36%) cases and 20 (37.74%) controls, SpO2 was increased. Koo et al. in 2017 found that out of 1227 patients with COPD, WBC was found to be increased according to the stage and severity of airflow limitation which was statistically significant with a P value of 0.03 (<0.05). They also found that WBC is further higher in COPD patients with smoking (P-<0.001) as compared to COPD alone. They also found a significant increase in WBC in COPD with DM as compared to non-diabetic COPD (P<0.001).(33). Higher WBC in DB-COPD patients is supposed to be due to increased risk of pulmonary infections due to DM, use of inhaled corticosteroids for the treatment for COPD that leads to the impaction of the causative organism in the lung that gives rise to leucocytosis.

CONCLUSION

We conclude that the presence of DM-COPD results from further decreases in FEV1, FVC, FEV1/FVC ratio, and PEFR on PFT, which needs to be confirmed further with DLCO and body plethysmography. An increase in HbA1C, FBS, and PMBS in DM-COPD further restrictive pattern along with obstructive pattern on spirometry. DM-COPD had a lower BMI than COPD alone, more affecting males with advanced age. A larger study is to be carried out with other subgroups to confirm this diagnosis. Further research on the pathophysiological basis to be done to better understand this condition. We conclude that COPD with DM had a significant decrease in PFT as compared to COPD alone. This proves that DM causes targeted damage to the lungs as poor glycaemic control leads to a further decrease in PFT. As pulmonary function can be the earliest symptom that detects the effects of DM on the lungs, it is advised that DM patients should undergo PFT regularly which detects the reduced pulmonary function in the initial stages.

LIMITATIONS:

Smoking duration, pack years and smoking index and duration of DM were not calculated. Exposures to environmental or occupational contaminants were also not measured. Further spirometry studies should be conducted in form of DLCO & Body Plethysmography for a

better understanding of lung function reduction in DM-COPD patients. DM patients must undergo periodic spirometry tests to assess the severity of lung function impairment.

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