Applied Cardiopulmonary Pathophysiology 16: 299-308, 2012

Study of pulmonary function tests in diabetics with COPD or asthma

G. P. Mishra[1], T.M. Dhamgaye[2], B.O. Tayade[3], B. Fuladi Amol[4], S. Agrawal Amit[5], D. Mulani Jasmin[6]

[1]Department of Chest & TB, Government Medical College, Nagpur, India, [2]Department of Chest & TB, BJ Medical College, Pune, India, [3]Department of Chest & TB, NKP Salve Medical College, Nagpur, India, [4]Dept. of Chest & TB, Government Medical College, Akola, India, [5]Resident, Maimonides Medical Center, New York, USA, [6]Rural Hospital, Rajegaon, Gondia, Maharashtra, India

Abstract

Introduction: The diagnosis of obstructive airway disease in diabetic patients may pose difficulties due the superimposition of restriction associated with diabetes on the pure obstructive pattern predominantly found in these patients. *Aims:* To evaluate the status of pulmonary function in diabetics (NIDDM – Non Insulin Dependent Diabetes Mellitus) with COPD (Chronic Obstructive Pulmonary Disease) or asthma. *Methods:* 45 Subjects (15 Diabetics with COPD, 15 Diabetics with Asthma & 15 healthy non diabetic, non smoking subjects with no chest complaints taken as the control group) underwent clinical evaluation, biochemical assessment of glycemic control, pulmonary function tests (Spirometry, DLCO and plethysmography lung volume measurements). *Results:* Spirometry showed pure obstruction in 20% patients whereas 66.67% patients had restriction which was confirmed in 20% on plethysmography. COPD patients had decreased DLCO/VA% (% Diffusion Lung Capacity of Carbon Monoxide corrected for Alveolar Volume) ($P < 0.0001$), increased TLC % (Total Lung Capacity) ($P < 0.05$), RV/TLC % (Residual Volume/ Total Lung Capacity %) ($P < 0.0001$) along with increased severity of airflow limitation (measured by FEV1% (Forced Expiratory Volume in 1st second)) which correlated with DLCO/VA % ($P < 0.05$). Asthmatics had near normal DLCO/VA%, TLC%, increased RV/TLC% ($P < 0.05$) & also demonstrated correlation of FEV1% with duration of diabetes ($P < 0.05$) and RV/TLC% ($p < 0.05$) & also of FVC % (Forced Vital Capacity %) with duration of diabetes ($P < 0.05$). *Conclusion:* Diabetics with COPD or asthma showed variable pulmonary function findings rather than the expected pure obstructive pattern and FEV1% and FVC% decline associated with diabetes might be responsible for these variable spirometric findings in addition to the severity of the airway disease.

Key words: Diabetes, COPD, Asthma, Pulmonary Function Test, DLCO, Spirometry, Plethysmography

Introduction

The interest in the relationship between diabetes and obstructive lung diseases has been pursued only recently. [1-4] The prevalence of asthma is significantly higher in patients with type II diabetes mellitus (DM), independent of other comorbid conditions. [1] Chronic obstructive pulmonary disease (COPD) may be a risk factor for developing NIDDM (Non Insulin Dependent Diabetes Mellitus). [2] Also hyperglycemia is associated with adverse clinical outcomes in patients with acute exacerbations of COPD. [3] Several prospective studies have found that impaired pulmonary function may increase the risk for developing

diabetes. [5] The pulmonary function in diabetics is characterized by restrictive lung defect. [6]

The assessment of pulmonary function parameters is important in diagnosis of COPD or asthma. The diagnosis of obstructive airway disease in diabetic patients may pose difficulties due the superimposition of restriction associated with diabetes on the pure obstructive pattern predominantly found in these patients. Thus the effect of already reduced lung functions associated with diabetes on diagnosing COPD or asthma in diabetic patients needs to be studied. With this background this study was undertaken to determine the pulmonary functions in diabetics (NIDDM) with COPD or asthma.

Materials and Methods

The study was conducted during July 2006 to December 2008. The study was carried out after approval from the institutional ethical committee and with fully informed written consent from the subjects.

The following three groups of subjects were included: 15 Type 2 DM patients with Chronic Obstructive Pulmonary Disease, 15 Type 2 DM patients with asthma & a control group of 15 healthy non diabetic, non smoking subjects with no chest complaints. A total of 45 consecutive subjects were included in the study depending on the criteria till the sample size of each group was met. All type 2 diabetic patients with COPD or asthma were included in the study. The patients were recruited as per the following criteria: 1. Diabetes Mellitus [7] : Symptoms of diabetes plus casual plasma glucose concentration ≥ 200 mg/dl or fasting plasma glucose ≥ 126 mg/dl or two-hour plasma glucose 200 mg/dl during an oral glucose tolerance test. 2. COPD: [8] Post bronchodilator FEV1/FVC <70 %, post bronchodilator change in FEV1 < 12% & clinical correlation (exposure to cigarettes; and/or environmental or occupational pollutants; and/or presence of cough, sputum production or dyspnoea). 3. Asthma: [9] Documented history of reversible airway obstruction based on FEV1 or post bronchodilator change in FEV1 ≥ 12% and ≥ 200ml & clinical correlation (episodic breathlessness, wheezing, cough, and chest tightness). Subjects with gross abnormalities of the vertebral column or thoracic cage, neuromuscular disease, malignancy, recent myocardial infarction within one month, recent eye surgery, stroke affecting the face, major psychiatric disorder (e.g. claustrophobia) and those who had undergone major abdominal or chest surgery were excluded from participating in the study. Also pregnancy, age < 18 yrs and evidence of any other pulmonary lesion on chest radiograph were other exclusion criteria. All patients with present or past history of smoking were excluded from the group of diabetic patients with asthma.

After detailed clinical assessment all the subjects underwent the following investigations.

Biochemical analysis of glycemic control: Fasting blood sugar & glycosylated haemoglobin (HbA1C) (by High performance liquid chromatography (HPLC) method) were measured as an indicator of glycemic control.

Pulmonary function tests: Pulmonary functions including spirometry, DLCO [Diffusion Lung Capacity for Carbon Monoxide measured using single breath technique] and plethysmography lung volume measurements were measured on Elite series body plethysmograph (Medical Graphics Corporation, USA; Software: Breeze Suite Version 6.2C). All the Pulmonary Function Tests were performed and interpreted as per the ATS criteria. [10-12]

Statistical Analysis

One-way analysis of variance (ANOVA) was used to compare the mean values in the three groups. In case of overall statistical significance in ANOVA, Student's t test was used to compare pairwise means. For analy-

sis Chi square test was used for categorical variable. Pearson correlation coefficient was used to quantify the extent of relationship between individual categorical variables. All the statistical tests used for analysis were two-tailed. $p < 0.05$ was considered as statistically significant and $p < 0.0001$ was considered as statistically highly significant. SPSS software version 15.0 was used for all statistical analysis.

Results

In the study, 29 males (64.4%) and 16 females (35.6%) were included. Their demographic & biochemical profiles are presented in table 1. There was no significant difference in the age, sex & BMI distribution of individuals across the three groups. The mean fasting blood sugar level was increased in diabetics with COPD & diabetics with asthma when compared to healthy subjects ($p < 0.0001$). The mean HbA1c level was increased in diabetics with COPD & diabetics with asthma when compared to healthy subjects ($p < 0.05$).

Duration of Diabetes: Diabetics with COPD had a significantly longer mean duration of diabetes (5.7 years, 95% CI 3.7 years to 7.6 years) when compared to diabetics with asthma (3.2 years, 95% CI 2.5 years to 3.9 years) ($p < 0.05$).

Pulmonary Function Tests: The various pulmonary function test parameters have been presented in tables 2 & 3.

Types of spirometric abnormality (Table 4): Pure obstructive pattern on spirometry was seen in only 3 (20%) diabetics with COPD and 3 (20%) diabetics with asthma, whereas a significant proportion of patients had the probability of an additional restrictive component on spirometry (Diabetics with COPD: 12 (80%), diabetics with asthma: 8 (53.33%), overall: 20 (66.67%)). Out of the 20 (66.67%) diabetics having the probability of an additional restrictive component (either pure restriction or combined pattern) on spirometry, only 4 (20%) patients were confirmed to have such a pattern on total lung capacity measurements by plethysmography (NIDDM with COPD: 2(10%) and NIDDM with asthma: 2 (10%)). 4 (26.67%) of patients with NIDDM and asthma had normal spirometry.

The severity of airflow limitation (as determined by FEV1 %(Forced Expiratory Volume in 1st second)) (Table 5): Diabetics with COPD had increased severity of airflow limitation when compared to diabetics with asthma. Thus maximum diabetics with COPD had very severe or severe airflow limitation (11 (73.33%)), whereas maximum diabetics with asthma had either no spirometric abnormality or mild airflow limitation (7 (46.67%)).

Table 1: Demographic and Biochemical profile of the subjects.

Variable	Diabetics with COPD (Mean ± SD)	Diabetics with Asthma (Mean ± SD)	Healthy Subjects (Mean ± SD)	P Value
Gender				
Males	11	7	11	0.2119
Females	4	8	4	
Age (years)	61.4 ± 4.47	60.27 ± 7.45	47.87 ± 5.92	0.0695
BMI (Body Mass Index)	21.66 ± 3.95	20.64 ± 2.22	23.18 ± 1.94	0.6968
Fasting Blood Sugar (mg dl)	182.24 ± 33.93	126.29 ± 24.89	90.13 ± 3.08	<0.0001
HbA1c (%)	7.89 ± 1.23	7.22 ± 0.8	5.99 ± 0.348	0.0065

DLCO/VA % (% Diffusing Lung Capacity of Carbon Monoxide corrected for Alveolar volume) (Tables 2, 3 & 6): The DLCO/VA% was significantly decreased in diabetics with COPD as compared to diabetics with asthma or healthy subjects ($p < 0.0001$). There was no significant difference in DLCO/VA% between diabetics with asthma and healthy subjects ($p = 0.0571$).

Plethysmography lung volumes (TLC% (Total Lung Capacity %) & RV/TLC % (Residual Volume/Total Lung Capacity %)) (Tables 2, 3, 7 & 8): The TLC% was significantly increased in diabetics with COPD as com-

Table 2: Pulmonary function test parameters.

Variable		Diabetics with COPD		Diabetics with Asthma		Healthy subjects		p value
		Mean	95 %CI	Mean	95%CI	Mean	95%CI	
FEV1 (Forced Expiratory Volume in 1st Second)	Absolute (L)	0.901	0.74 to 1.06	1.187	0.92 to 1.46	2.248	1.90 to 2.59	
	% predicted	39.867	32.49 to 47.25	63.067	46.55to 79.58	81.333	75.34 to 87.33	<0.0001
FVC (Forced Vital Capacity)	Absolute(L)	1.851	1.59 to 2.11	1.813	1.38 to 2.25	2.814	2.33 to 3.3	
	% predicted	65.467	55.30 to75.63	73.067	58.93 to 87.20	83.8	76.940 to 90.660	0.0449
DLCO/VA (DLCO corrected for alveolar volume)	Absolute (ml/minute/mm of Hg)	3.032	2.48 to 3.58	4.427	4.06 to 4.8	4.917	4.53 to 5.31	
	% predicted	56.133	45.84 to 66.42	79.533	72.84 to 86.23	86.967	82.58 to 91.15	<0.0001
TLC (Total Lung Capacity)	Absolute(L)	6.499	4.67 to 8.33	4.253	3.56 to 4.95	4.495	4.08 to 4.91	
	% predicted	127.07	93.76 to 160.37	89.40	80.58 to 98.23	87.07	80.97 to 93.16	Mai 68
RV/TLC (Residual Volume/ Total Lung Capacity)	Absolute	64.2	58.2 to 70.2	55.8	47.7 to 63.9	33.7	31 to 36.3	
	% predicted	186.5	165.5 to 207.6	157.2	131.2 to 183.2	112.1	104.5 to 119.8	<0.0001

Table 3: Pulmonary function test parameters compared pairwise.

Parameters compared pairwise	P value		
	Diabetics with COPD & Diabetics with Asthma	Diabetics with Asthma & Healthy Subjects	Diabetics with COPD & Healthy Subjects
FVC%	0.3571	0.1540	0.0033
DLCO/VA%	0.0003	0.0611	<0.0001
TLC%	0.0264	0.6444	0.0172
RV/TLC%	0.0707	0.0013	<0.0001

pared to either diabetics with asthma ($p < 0.05$) or healthy subjects ($p < 0.05$). There was no significant change in TLC% in diabetics with asthma as compared to healthy subjects ($p = 0.6444$). The RV/TLC% was significantly increased in diabetics with COPD ($p < 0.0001$) or diabetics with asthma ($p < 0.05$) when compared to healthy subjects.

Correlation of severity of airflow limitation (as determined by FEV1%) with other parameters: Diabetics with COPD demonstrat-

Table 4: Types of spirometric abnormality.

Spirometric abnormality	Diabetics with COPD		Diabetics with Asthma		Healthy Subjects		Total	
	No.	%	No.	%	No.	%	No.	%
Obstruction	3	20	3	20	0	0	6	13.33
Restriction	11	73.33	3	20	4	26.67	18	40
Combined	1	6.67	5	33.33	1	6.67	7	15.56
No abnormality	0	0	4	26.67	10	66.67	14	31.11
Total	15	100	15	100	15	100	45	100

Table 5: Distribution of severity of spirometric abnormality.

Severity of spirometric abnormality	Diabetics with COPD		Diabetics with Asthma	
	No.	%	No.	%
No spirometric abnormality	0	0	4	26.67
Spirometric abnormality as per the severity (FEV1%)				
> 70 mild	0	0	3	20
60-69 Moderate	0	0	1	6.67
50-59 Moderately Severe	4	26.67	1	6.67
35-49 Severe	5	33.33	2	13.33
<35 Very severe	6	40	4	26.67
Total	15	100	15	100

Table 6: Distribution of DLCO/VA% (Diffusion Capacity of Lung for Carbon Monoxide corrected for Alveolar Volume %).

DLCO/VA%	Diabetics with COPD		Diabetics with Asthma		Healthy Subjects		Total	
	No.	%	No.	%	No.	%	No.	%
≥ 81	0	0	7	46.67	13	86.67	20	44.44
61-80	8	53.33	7	46.67	2	13.33	17	37.78
41-60	4	26.67	1	6.67	0	0	5	11.11
≤40	3	20	0	0	0	0	3	6.67
Total	15	100	15	100	15	100	45	100

ed significant correlation between FEV1% and DLCO/VA % ($r=0.751$, $p<0.05$).Diabetics with asthma demonstrated significant negative correlation of FEV1% with duration of diabetes ($r=-0.637$, $p<0.05$) and RV/TLC% ($r=-0.677$, $p<0.05$). Further diabetics with COPD demonstrated no significant correlation between FEV1% and fasting blood sugar levels, HbA1c levels, duration of diabetes, TLC%, RV% or RV/TLC%. Diabetics with asthma demonstrated no significant correlation between FEV1% and fasting blood sugar levels, HbA1c levels, TLC% or DLCO/VA%.

FVC % (Forced Vital Capacity %): Also diabetics with asthma demonstrated significant negative correlation of FVC% with duration of diabetes ($r=-0.52$, $p<0.05$). This correlation was not shown in diabetics with COPD.

Discussion

According to the literature review, to the best of our knowledge this is the first study to assess the complete pulmonary function tests (spirometry, DLCO & plethysmography lung volume measurement) in diabetics with COPD or asthma.

Dykstra et al. [13] in a study on 4,774 patients with COPD and asthma demonstrated that 39.2% patients had the probability of an additional restrictive component (either pure restriction or combined pattern) on spirometry. Of these patients, only 9.5% patients had a low TLC. In the present study, the high proportion of patients in this study having the probability of an additional restrictive component (either pure restriction or combined pattern) on spirometry (66.67%) and further confirmed by a low TLC (20%) could be due to the increased severity of disease as a reduction in FVC could be due to the hyperinflation with impingement of the RV (Residual Volume) on the FVC. Another possible reason for such a high proportion of these patients could be the independent decline of FEV1 and FVC known to be associated with diabetes. [6, 14-16] This could be a significant cause in the present study as the study population included diabetics with COPD or asthma. Also a decrease in TLC is known to be

Table 7: Distribution of TLC% (Total Lung Capacity %).

TLC%	Diabetics with COPD		Diabetics with Asthma		Healthy Subjects		Total	
	No.	%	No.	%	No.	%	No.	%
>120	5	33.33	0	0	0	0	5	11.11
80-120	8	53.33	12	80	13	86.67	33	73.33
<80	2	13.33	3	20	2	13.33	7	15.56
Total	15	100	15	100	15	100	45	100

Table 8: Distribution of RV/TLC% (Residual Volume / Total Lung Capacity %).

RV/TLC%	Diabetics with COPD		Diabetics with Asthma		Healthy Subjects		Total	
	No.	%	No.	%	No.	%	No.	%
≤ 120	0	0	4	26.67	11	73.33	15	33.33
>120	15	100	11	73.33	4	26.67	30	66.67
Total	15	100	15	100	15	100	45	100

independently associated with diabetes probably due to pulmonary microangiopathy associated with diabetes. [6, 17]

A high proportion of patients with diabetes and asthma in the present study had normal spirometry or mild airflow limitation and also diabetes has been shown to be associated with mild decline in FEV1 and FVC, hence the correlation of FEV1 and FVC with the duration of diabetes in patients with diabetes and asthma could be demonstrated. [6, 14-16]

The diabetics with COPD had a high proportion of patients with severe and very severe airflow limitation and this could be the possible cause that the mild reduction in FEV1 and FVC, known to be associated with diabetes could not be demonstrated in diabetics with COPD. [6, 14-16]

In the present study diabetics with COPD had a significantly longer mean duration of diabetes when compared to diabetics with asthma and this could be the cause of greater decline in FEV1 and FVC in relation to the duration of diabetes in these patients. [6, 14-16] Also there have been documented reports of increased inflammatory markers like leukotriene B4 in subjects with chronic obstructive pulmonary disease (COPD) who also had diabetes, compared with COPD patients and asthmatics without diabetes thus leading to more severe airflow limitation in these patients. [6]

Sin et al. [18] demonstrated that FEV1% was lower in COPD patients than in asthmatics in his study on elderly subjects with late onset asthma and COPD. Similar findings were seen in diabetics with COPD or Asthma in this study.

Davis et al. [19] demonstrated that the mean FEV1 % and mean FVC% were reduced and diabetes duration was significantly associated with FEV1 % and had borderline associations with FVC % in diabetics. In the present study, diabetics with asthma, a high proportion of whom had normal spirometry or mild airflow limitation, demonstrated a similar finding. The decline in FEV1 and FVC associated with duration of diabetes has been attributed to the pulmonary microangiopathy in diabetes characterized by thickened alveolar capillary walls, the pulmonary arteriolar walls and the alveolar walls along with narrowing of the alveolar space, the flattening of the alveolar epithelium and the expansion of the interstitium. [6, 20]

Previous studies have demonstrated that DLCO is decreased in diabetics and also in COPD patients while it is normal or increased in asthmatics. [6, 17, 21, 22] In COPD patients, the decrease in DLCO is thought to be directly related to the loss of alveolar-capillary surface area that is associated with emphysema. [22] The findings of the present study are in confirmation with these findings.

Sin et al. [18] demonstrated that patients with COPD had significantly decreased DLCO/VA when compared to asthmatic patients. Similar findings were noted in the present study except that the mean values of DLCO/VA % in the present study were lower than those demonstrated by Sin et al. The possible reason for the lower mean values of DLCO/VA% in the present study could be that the COPD and asthmatics in the present study had diabetes in addition which is known to be independently associated with a decreased DLCO. [6, 19, 20, 22, 23]

The pathophysiological mechanism for reduction of DLCO in diabetes mellitus has been attributed to pulmonary microangiopathy. [6, 20, 23]

Previous studies have demonstrated a significant positive correlation of FEV1% with DLCO in COPD patients. Diabetics with COPD in the present study showed a similar correlation between FEV1% and DLCO/VA %. [24-27]

Previous studies have demonstrated that COPD patients have more severe airways obstruction and more hyperinflation when compared to those reporting asthma only, they have greater lung volumes and have a significantly increased RV as compared to asthmatics.[13,27,28] The findings of the present study are in agreement with the previous studies. Evidence of hyperinflation on

plethysmography was present in 100 % of diabetics with COPD and 73.33% of diabetics with asthma. The higher RV in patients with airflow obstruction due to COPD suggests that parenchymal destruction is present in COPD. [28]

Previously it has been shown that the degree of hyperinflation is significantly associated with the degree of airways obstruction in patients with obstructive airway disease, as indicated by the FEV1%. Also the RV or the RV/TLC is much more sensitive than the TLC to the degree of airways obstruction. [13] In the present study, in diabetics with asthma there was significant correlation between FEV1% and RV/TLC% which are in confirmation with the previous study. [13] In the present study there was no correlation of FEV1% with RV/TLC in patients with diabetes and COPD unlike the previous findings [13] which demonstrated a similar correlation in patients with COPD. The possible reason for this could be that the diabetics with COPD had a high proportion of patients with severe and very severe airflow limitation and small errors in the measurement of lung volumes using body plethysmography (without using an oesophageal balloon to estimate alveolar pressure changes) are also known to occur in patients with severe airways obstruction. [13] Also pulmonary microangiopathy in diabetes in combination with parenchymal destruction of COPD could be a cause that the severity of airflow limitation was increased in diabetics with COPD as compared to diabetics with asthma [6, 20, 22, 23, 28] supported by the finding in the present study that diabetics with COPD had a significantly longer mean duration of diabetes when compared to diabetics with asthma.

Our study has several limitations. Firstly the number of patients studied is small but the resource limited setting led to an overall small number of advanced pulmonary function tests that could be conducted. Secondly alveolar pressure estimates by oesophageal balloon were not carried out due to lack of testing facility. This could have enhanced the accuracy of plethysmography lung volume measurements. Thirdly the inclusion of HbA1C as a defining criterion for diabetes could have broadened the spectrum of diabetic patients in the current study. The use of HbA1C to diagnose diabetes, with a cut point of $\geq 6.5\%$ has recently been added as a diagnostic criterion for diabetes. [29] It is therefore desirable that all future studies on this subject also include this additional and important diagnostic criterion. In the current study, HbA1C was measured in all patients but it was not included as a diagnostic criterion since it was based on the pre-existing definition of diabetes prior to the addition of this recent additional diagnostic criterion for diabetes. [7]

The present study suggests that the decrease in FEV1% and FVC% associated with diabetes might be responsible for variable spirometric findings in addition to the severity of the airway disease, thus necessitating the need for confirmation with further pulmonary function tests in the form of DLCO and lung volume measurements with body plethysmography. This factor must be considered in interpreting spirometric findings in diabetics with COPD or asthma since only a minority of these patients have shown pure obstructive pattern on spirometry. A larger prospective study with long observational course in more varied subgroups needs to be carried out in these patients to confirm these findings. Also further research in the form of pathophysiological studies could lead to a better understanding of this condition.

Conflict of interest: Nil
Funding: Nil

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Address for correspondence:
Dr. Gyanshankar P. Mishra
Assistant Professor
Dept. Of Chest & TB
TB Ward premises
Government Medical College
Nagpur, Maharashtra, India - 440003
gpmishra81@gmail.com