

Pulmonary function abnormalities and Type 2 Diabetes Mellitus – a cross-sectional study

S Philip, A Basheer, K Thomas, R Kandasamy, K H Kisku

Abstract

Despite rich microvascular networks in the lungs, studies are inconsistent regarding an association between diabetes and pulmonary function abnormality. A cross sectional study was conducted among 90 diabetic patients and an equal number of age and gender matched non-diabetic adults. Prevalence of pulmonary function test (PFT) abnormalities was estimated in both groups. Logistic regression was used to determine independent associations between diabetes and its complications considering other risk factors for altered lung function. PFT were abnormal in 71 (79%) (95% CI= 69.0 – 86.0) of 90 diabetic and 52 (58%) of non-diabetic patients ($p=0.02$). There were 42 (47%) diabetic adults with a restrictive pattern (95% CI= 36.0-57.4) while 29 (32%) had an obstructive pattern (95% CI= 22.9-43.0). Presence of diabetes, age, female sex, glycosylated hemoglobin and body mass index (BMI) were associated with abnormal PFT in univariate analysis, while only age, female sex and BMI had significant associations on multivariate analysis. To conclude, there was no independent association between diabetes status and abnormal lung function. Increasing age, higher BMI and female sex were independent risk factors for pulmonary dysfunction.

Introduction

About 7% of Indian adults suffer from type 2 diabetes (T2DM), making India a country with more diabetic patients than any other on the globe. It is well established that poor glycaemic control leads to microvascular and macrovascular complications. Although the functional disturbances that ensue from pathophysiologic alterations in the microvasculature has been extensively studied in the kidneys, retina and nerves, the effect of diabetes

on the lung, another organ with a rich microvascular network has not been investigated with much interest. Some studies have suggested that pulmonary function is compromised significantly in persons with T2DM,^{1,2} however an independent association between diabetes and lung function abnormalities has not been revealed convincingly. Therefore, we aimed to determine the association of pulmonary function with diabetes and the correlation of pulmonary function abnormalities with microvascular complications.

Patients and methods

This was a cross sectional comparative study carried out in a tertiary care teaching hospital in Pondicherry, India. The study was conducted between December 2014 and April 2016. Eligible participants included 90 adults below 60 years of age with T2DM attending the outpatient clinics or admitted to the wards during the study period, and an equal number of non-diabetic adults matched for age and gender who served as the comparative controls. Persons with chronic lung diseases like asthma, chronic bronchitis and bronchiectasis, restrictive airway conditions like scoliosis, pulmonary tumours and respiratory infection (upper and lower respiratory tract infection), active tuberculosis, occupational lung diseases, type 1 diabetes, glomerular filtration rate < 60 ml/minute, pregnant women and smokers were excluded from the study.

The diabetic subjects underwent baseline evaluation for microvascular complications including nephropathy (using spot albumin to creatinine ratio), retinopathy (using direct ophthalmoscopy by the same ophthalmologist for all subjects) and neuropathy (defined clinically by absence of deep tendon reflexes in the legs, diminished sensation including touch as assessed by cotton wool, pinprick or pressure sensation, distal vibratory sensation as assessed by graduated tuning fork of 128 Hz, and joint position sense). Based on these assessments they were further subdivided into those patients with microvascular complication(s) and those without (45 subjects each).

Biochemical investigations included fasting and post-prandial blood glucose, glycosylated haemoglobin (HbA1c), fasting lipid profile, blood urea and serum creatinine. Pulmonary function test was performed by a trained spirometrist according to American Thoracic Society (ATS) criteria in all the study subjects using the Ndd Easyone Pro computerised spirometer. All the sub-

Dr. Susan Philip, Senior Resident, Department of General Medicine; Dr. Aneesh Basheer, Associate Professor, Department of General Medicine; Dr. Kurien Thomas, Professor, Department of General Medicine, Dr. Ravichandran Kandasamy, Assistant Professor, Department of Biostatistics, Dr. King Herald Kisku, Professor, Department of Pulmonary Medicine: all, Pondicherry Institute of Medical Sciences, Kalapet, Pondicherry, India. Corresponding Author: Dr. Aneesh Basheer, email: basheeraneesh@gmail.com

jects were asked to sit in an upright position and perform spirometry three times at intervals of 15 minutes, and the best of the three was taken into account. Parameters measured included Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 second (FEV1), FVC ratio, Peak Expiratory Flow Rate (PEFR), Forced Expiratory Flow at 25 – 75% of vital capacity with calculation of their percentage predictive values. The diffusing capacity of lung for carbon monoxide (DLCO), alveolar ventilation (VA) and DLCO/VA ratio were determined by a single breath carbon monoxide (CO) diffusion test.

Assuming a prevalence of pulmonary function abnormality in 25% of patients with T2DM and a precision of 9%, a sample size of 90 was determined for diabetic subjects. An equal number of controls were used for comparison. The clinical characteristics of the study patients were expressed using mean and standard deviation for continuous variables and percentage for dichotomous and categorical data. To find associations, simple logistic regression was done and those with significant or near significant *p* values (*p*<0.2) were selected for multivariate analysis. Multivariate analysis was done using the ENTER method, and a *p* value less than 0.05 was considered significant. All the data were entered in Microsoft Excel and statistical analysis was done using SPSS version 20 for windows.

The Institute Ethics Committee approved the study [IEC no. RC/14/70]. Written informed consent was taken from the study subjects.

Results

Patients with FEV1/FVC ratio of less than 80% were classified as those with an obstructive abnormality while patients with FEV1/FVC ratio more than 80% included those with restrictive abnormality or normal pulmonary function. In the latter group, if DLCO was less than 75% of predicted, they were classified as having restrictive abnormality.

Baseline characteristics of the diabetic patients and non-diabetic controls are depicted in Table 1.

Among the 90 diabetic patients, 71 (79%) patients had abnormal PFTs (95% CI= 69.0 – 86.0), and 42 of these patients (47%) had a restrictive pattern of abnormality (95% CI= 36.0-57.4), while 29 patients (32%) had an obstructive pattern (95% CI= 22.9-43.0). In patients without diabetes, 52 (58%) had abnormal pulmonary function; 24 (27%) had an obstructive pattern (95% CI = 18-37.2) while 28 (31%) had a restrictive abnormality (95% CI = 22-41.8; *p*=0.002 .)

Risk factors associated with pulmonary function abnormalities

On univariate analysis, apart from diabetes the following factors were significantly associated with abnormal PFTs – female gender, BMI, age and HbA1c. However, on multivariate analysis, only female gender, age and BMI retained significant associations with PFT abnormality (Table 2).

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Among the 90 diabetic adults included in the study, 45 had microvascular complications – 23 had isolated neuropathy, 13 had isolated retinopathy, 6 had both neuropathy and retinopathy while 3 had both neuropathy and nephropathy. An abnormal PFT was found in 87% of diabetic patients with microvascular complications compared to 71% of those without any microvascular complications (*p*=0.12). In diabetic patients with microvascular complications and PFT abnormalities, the predominant abnormality detected was restrictive (62%).

We performed univariate and multivariate analysis to determine any association between various risk factors and PFT abnormalities within the diabetic cohort (Table 3). Microvascular complications did not have any association with PFT abnormality in diabetic patients [OR 1.96 (95% CI: 0.54-7.13); *p*=0.308]. Only female sex showed a significant association after multivariate analysis while LDL cholesterol had a near significant association (*p*=0.071) with PFT abnormality among diabetics.

Discussion

This study has identified that the prevalence of pulmonary function abnormalities in diabetic patients is 79% with most having a restrictive pattern. Compared to controls there was a significant overall reduction of pulmonary function, as well as individual parameters like FEV1, FVC and PEFR. The DLCO was also found to be lower in diabetic patients indicating significant impairment of alveolar gas exchange. However, this study did not find evidence of an independent association between diabetes and PFT abnormality. Nonetheless females were found to be at higher risk of developing abnormal PFT. High LDL and BMI also seemed to be associated with pulmonary dysfunction in diabetic patients.

The prevalence and distribution of PFT abnormalities in our study population parallels that of several other investigators.^{1,3,4} Of note, an Indian study found a restrictive pattern in 48% of diabetic patients, very similar to the finding of this study.⁵ The proposed mechanism is microangiopathic changes including basal lamina thickening and fibrosis, eventually leading to restrictive lung defects.⁶ These changes may also explain the significant reduction in DLCO observed in diabetic patients with pulmonary function abnormalities.

Despite a significant increase in PFT abnormalities in diabetic adults compared to controls, we could not establish an independent association between diabetes and abnormal pulmonary function. Most studies in the past have attempted comparison of the spirometry variables between diabetic and non-diabetic patients, but very few have done an adjusted analysis as in this study. Notably a large cross-sectional and prospective study on diabetic and non-diabetic counterparts provided some interesting data.⁷ Similar to our findings, investigators were able to show a significantly lower pulmonary function (evidenced by lower FEV1 and FVC) in diabetic compared to non-diabetic adults. However, unlike in our study,

Table 1. Baseline characteristics of diabetic and non-diabetic patients in the study

| Characteristic | Diabetic patients (n=90) | Controls (n=90) |
|--------------------------------------|--------------------------|-----------------|
| Age (years) | 49 ± 8 | 49 ± 8 |
| Body mass index (kg/m ²) | 24 ± 4.6 | 24 ± 5 |
| Fasting blood glucose (mmol/L) | 9.3 ± 3.2 | 5.0 ± 0.6 |
| Postprandial blood glucose (mmol/L) | 15.9 ± 5 | 6.8 ± 1.1 |
| HbA1c (%) | 8.7 ± 1.7 | 5.4 ± 0.4 |
| Blood urea (mmol/L) | 3.7 ± 1.4 | 3.2 ± 0.8 |
| Serum creatinine (mmol/L) | 71 ± 27 | 71 ± 18 |
| Total cholesterol (mmol/L) | 4.7 ± 1.0 | 4.7 ± 1.0 |
| LDL cholesterol (mmol/L) | 3.1 ± 1.0 | 3.1 ± 0.9 |
| Triglycerides (mmol/L) | 1.9 ± 0.7 | 1.7 ± 0.7 |

All values are mean ± S.D.

Table 2. Logistic regression analysis of (univariate and multivariate) of risk factors associated with PFT abnormalities

| Risk factors | Univariate | | Multivariate | |
|--------------|------------------|---------|------------------|---------|
| | OR (95% CI) | p value | OR (95% CI) | p value |
| Diabetes | 2.73 (1.41-5.26) | 0.003 | 1.69 (0.50-5.65) | 0.013* |
| Age | 1.05 (1.01-1.10) | 0.017 | 1.06 (1.01-1.11) | 0.002* |
| Sex (female) | 4.20 (1.83-9.61) | 0.001 | 4.04 (1.64-9.90) | 0.043* |
| BMI | 0.95 (0.89-1.01) | 0.129 | 0.92 (0.85-0.99) | 0.507 |
| HbA1c | 1.31 (1.09-1.57) | 0.004 | 1.11 (0.81-1.51) | |

*Significant association on multivariate analysis [Risk factors with significant or near significant association (p<0.2) on univariate analysis were included in multivariate analysis].

Table 3. Univariate and multivariate analysis of association between risk factors and PFT abnormality among diabetic patients (n=90)

| Risk factors | Univariate | | Multivariate | |
|-----------------------------|-------------------|---------|-------------------|---------|
| | OR (95% CI) | p value | OR (95% CI) | p value |
| Microvascular complications | 2.64 (0.90-7.73) | 0.076 | 1.96 (0.54-7.13) | 0.308 |
| Age | 1.01 (0.95-1.08) | 0.745 | | |
| Sex | 3.45 (1.04-11.41) | 0.043 | 3.72 (1.05-13.23) | 0.042* |
| BMI | 0.95 (0.86-1.06) | 0.363 | | |
| HbA1c | 1.21 (0.88-1.66) | 0.235 | 1.06 (0.73-1.53) | 0.743 |
| Duration of diabetes | 1.01 (1.0-1.02) | 0.239 | 1.00 (1.0-1.01) | 0.384 |
| Hypertension | 1.55 (0.40-6.0) | 0.525 | | |
| Total cholesterol | 1.01 (0.99-1.02) | 0.282 | | |
| Triglycerides | 1.00 (0.99-1.01) | 0.666 | | |
| HDL | 1.00 (0.94-1.06) | 0.980 | | |
| LDL | 1.02 (1.00-1.03) | 0.021 | 1.02 (1.0-1.03) | 0.071* |

OR = Odds Ratio; CI = confidence intervals

this reduction was independent of other risk factors including age, HbA1c and duration of diabetes. Moreover, due to the prospective design and relatively good follow up, they were able to demonstrate a faster decline in FVC in diabetic compared to non-diabetic patients. On the other hand, a prospective study on Danish adults could not replicate the marked differences in decline

of lung function between diabetic and non-diabetic patients on follow up for 15 years.⁸ Such conflicting results even among prospective studies indicate that though lung function abnormalities are much higher in a diabetic population, establishing an independent association between them (let alone causation) has not been an easy task. Our findings echo the same complexity of the issue.

Shravya et al demonstrated a higher risk among females for development of pulmonary dysfunction,⁹ a finding which we also were able to replicate. However, the association of PFT abnormality with high BMI inferred from this study has not been consistent across studies in the past. While data from a Nigerian study showed that restrictive abnormalities of lung function in T2DM were more common among persons with a high BMI.¹⁰ A study from Trinidad concluded that there was no association between spirometric abnormalities and BMI in diabetic patients.¹¹

Although PFT abnormality was associated with microvascular complications in patients in our study, it was not statistically significant. Likewise, some studies using DLCO measurements were unable to establish any such association with microvascular complications.¹²⁻¹⁴ Asanuma and coworkers have however shown that reduced DLCO in diabetic patients is associated with microvascular complications, again adding to the uncertainty regarding the very existence of microangiopathy in the lungs and its possible effects on lung function.¹⁵ Thus, the theoretically plausible association between lung dysfunction and other microvascular complications (derived by the assumption that microvasculature of the lung must also be affected by diabetes) remains unproven.

The same uncertainty and discordance exists among studies with regard to effect of glycaemic control and duration of diabetes on pulmonary function abnormality. While several

studies reported that poor glycaemic control is associated with a reduced DLCO, results from our study and others like Davis et al and Shah et al have found no association between PFT abnormality and glycaemic status.¹⁶⁻¹⁹ Kumari and colleagues concluded that the restrictive pattern of lung dysfunction worsened as the duration of diabetes increased,⁴ while we were unable to

demonstrate an independent association with duration of diabetes. Disparity in results might be explained to some extent by the heterogeneity in parameters used to assess lung function abnormality, as well as the lack of adequate follow-up data on glycaemic control.

The major strength of this study is the relatively larger sample size that has been studied compared to most other studies from India dealing with this issue. In addition, we employed rigorous statistical methods to determine whether an independent association exists between diabetes and PFT abnormality, which many other investigators have not attempted. Nonetheless, the cross-sectional design could have led to restrictions on availability of follow-up data. A prospective design could have provided more valid results on association with duration of disease and glycaemic control. Moreover, the lack of independent association with age, gender and BMI on multivariate analysis suggests that there could be other unidentified and untested confounders that contributed to the excess PFT abnormalities in diabetic patients.

In conclusion we have only been able to demonstrate a significantly higher prevalence of PFT abnormalities in diabetic adults compared to healthy non-diabetic patients. The results of this study highlight the need for optimally designed prospective studies with adequate follow up to ascertain whether diabetes directly leads to pulmonary function abnormalities, and whether such abnormalities closely parallel well-established microvascular complications of diabetes like nephropathy, neuropathy and retinopathy.

Author declaration

The authors confirm that they have no competing interests to declare; that no animals were used in the research, and that informed consent was obtained from patients (documentary evidence on this provided to the publisher).

References

- Shah S, Sonawane P, Vaidya S, Salvi S, Nahar P. Pulmonary function tests in type 2 diabetes mellitus and their association with glycemic control and duration of the disease. *Lung India*. 2013;30:108-112.
- Uz-Zaman S, Banerjee J, Singhamahapatra A, et al. Assessment of lung function by spirometry and diffusion study and effect of glycemic control on pulmonary function in type 2 diabetes mellitus patients of the eastern India. *J Clin Diagn Res*. 2014; 8:BC 01-04. doi: 10.7860/JCDR/2014/9756.5076.
- Irfan M, Jabbar A, Haque A, Awan S, Hussain S. Pulmonary functions in patients with diabetes mellitus. *Lung India*. 2011;28:89-92.
- Kumari K, Nataraj SM, Devaraj HS. Glycemic control and pulmonary function tests in type 2 diabetes Mellitus patients: Do they correlate? *Ind J Publ Hlth Res Dev*. 2013;4:124-128.
- Singh Y, Kumari S. The pulmonary function tests in patients with diabetes mellitus and non-diabetes people of Ajmer, Rajasthan. *Int J Basic Appl Med Sci*. 2015;5:8-13.
- Weynand B, Jonckheere A, Frans A, Rahier J: Diabetes mellitus induces a thickening of the pulmonary basal lamina. *Respiration* 1999;66:14 -19
- Yeh H, Punjabi NM, Wang NY, et al. Cross-sectional and prospective study of lung function in adults with type 2 diabetes: The Atherosclerosis Risk in Communities (ARIC) study. *Diabetes Care*. 2008;31:741-6.
- Lange P, Parner J, Schnohr P, Jensen G. Copenhagen City Heart Study: longitudinal analysis of ventilatory capacity in diabetic and non-diabetic adults. *Eur Respir J*. 2002;20:1406-1412.
- Keerthi G S. Deterioration of pulmonary functions in type 2 diabetes mellitus. *IOSR J Pharm Biol Sci*. 2012;1:39-43.
- Adeyeye OO, Ogbera OA, Dada AO, Bamisile RT, Brodie M A. Correlates of abnormal pulmonary function tests in persons with type 2 diabetes mellitus. *J Pulm Resp Med*. 2014;05:1-4.
- Nayak BS, Sakamuri SM, Guerra C, et al. Evaluation of pulmonary dysfunction among persons with type 2 diabetes in Trinidad. *Int J Res Dev Pharm L Sci*. 2013;2:317-320.
- Agarwal AS, Fuladi AB, Mishra G, Tayade BO. Spirometry and diffusion studies in patients with type-2 diabetes mellitus and their association with microvascular complications. *Indian J Chest Dis Allied Sci*. 2010;52:213-216.
- Sinha S, Guleria R, Misra A, et al. Pulmonary functions in patients with type 2 diabetes mellitus and correlation with anthropometry and microvascular complications. *Indian J Med Res*. 2004;119:66-71.
- Boulbou MS, Gourgoulanis KI, Klisiaris VK, et al. Diabetes mellitus and lung function. *Med Princ Pract*. 2003;21;12:87-91.
- Asanuma Y, Fujiya S, Ide H, Agishi Y. Characteristics of pulmonary function in patients with diabetes mellitus. *Diab Res Clin Pract*. 1985;1:95-101.
- Anandhalakshmi S, Manikandan S, Ganeshkumar P, Ramchandran C. Alveolar gas exchange and pulmonary functions in patients with type II diabetes mellitus. *J Clin Diagn Res*. 2013;7:1874-1877.
- McKeever TM, Weston PJ, Hubbard R, Fogarty A. Lung function and glucose metabolism: an analysis of data from the Third National Health and Nutrition Examination Survey. *American J Epidemiol*. 2005;161:546-556.
- Davis WA, Knuiman M, Kendall P, Grange V, Davis TME. Glycemic exposure is associated with reduced pulmonary function in type 2 diabetes: The Fremantle Diabetes Study. *Diabetes Care*. 2004;27:752-757.
- Davis TME, Knuiman M, Kendall P, Vu H, Davis WA. Reduced pulmonary function and its associations in type 2 diabetes: The Fremantle Diabetes Study. *Diab Res Clin Pract*. 2000;50:153-159.