

Research Article

Assessment of pulmonary function in patients with type 2 diabetes mellitus: a case-control study

Dhiraj Kapoor¹, Pankaj Kumar^{1*}, Asha Ranjan¹, Kailash Nath Sharma¹,
Varun Deep Dogra¹, Rekha Bansal², K. K. Sharma³, Dinesh Kumar⁴

¹Department of Medicine, Dr. Rajendra Prasad Government Medical College, Kangra, H.P., India

²Department of Chest and Tuberculosis, Dr. Rajendra Prasad Government Medical College, Kangra, H.P., India

³Department of Biochemistry, Dr. Rajendra Prasad Government Medical College, Kangra, H.P., India

⁴Department of Community Medicine, Dr. Rajendra Prasad Government Medical College, Kangra, H.P., India

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*Correspondence:

Dr. Pankaj Kumar,

E-mail: pakugu2003@yahoo.co.in

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ABSTRACT

Background: As other microvascular complications, respiratory involvement is far less studied among patients with type-2 Diabetes Mellitus (DM). Objective: to study the extent of pulmonary function limitation among patients with type-2 DM.

Methods: Hospital based matched case-control study.

Results: Total of 90 cases and 90 controls matched for age, sex, height and weight were recruited. Patients with DM had neuropathy [63.3% (57; male=27: Female: 30)], retinopathy [44.4% (40; male=22: Female: 18)], nephropathy [41.1% (37; male=17: Female: 20)] and microalbuminuria [14.4% (13; male=5: Female: 8)]. All cases and 88 controls observed with FEV1:FVC ratio of >70.0%, further assessment for delineation of normal and restrictive pattern patients with high level of predicted values of FEV1 as compare to FVC showed that significantly (P = 0.00) more (Cases: 76.6%; Controls: 42.2%) cases had FEV1 >FVC predicted levels as compare to controls, means among diabetics odds of restrictive pattern of lung abnormality is four times (OR: 4.4; CI: 2.3-8.5) more as compare to non-diabetics. In addition a long duration of DM was significantly (r: 0.39; P = 0.00) positively correlated with lung dysfunction.

Conclusion: Patients with type 2 DM patients as compare to its controls observed with restrictive pattern of lung dysfunction.

Keywords: Pulmonary function test, Diabetes mellitus

INTRODUCTION

Type 2 is most common (90.0%) form of diabetes mellitus and is main driver of the diabetes epidemic, which is affecting 5.9% of the world's adult population with almost 80% of the total in developing countries. According to International Diabetes Federation (IDF), 366 million people had diabetes in 2011 and by 2030 this will rise to 552 million. Most of diabetics belonged to age group of 40 to 59 years and caused 4.6 million deaths in

2011 alone.¹ Due to large population, diabetes epidemic is much more pronounced in India where over 61 million diabetics resides. It is estimated that by 2030, India's diabetes burden is expected to cross the 100 million mark. Apart from morbidity, India is also the largest contributor to regional mortality with 983000 deaths caused due to diabetes in 2011.¹

Diabetes causes end organ dysfunction due to macrovascular and microvascular complications due to

accelerated atherosclerosis. Long standing disease, after 15 years, causes visual loss in 2% of patients and 10.0% develop severe visual impairment. It causes renal failure among 10-20% of patients and peripheral neuropathy among 50.0% patients with uncontrolled diabetics.² Complications arises due to formation of Advanced Glycation End products (AGEs), activation of protein kinase C and glucose metabolism by sorbitol pathway.²

Effect of diabetes on alveolar capillary network of lungs was less well studied. Due to its large reserve, the substantial loss of the microvascular bed can be tolerated without developing dyspnea. As a result, pulmonary diabetic microangiopathy may remain under-recognised clinically. Since normal lung mechanics and gas exchanges are influenced by the integrity of the pulmonary connective tissue and the microvasculature, abnormalities in either of these structural components of the lung may lead to the development of measurable abnormalities of lung function. The reduced lung functions in patients with diabetes appear to be inversely related to blood glucose levels, duration of diabetes and its severity.⁴ Studies evaluating the pathophysiology of lung impairment in diabetes has identified several potential mechanisms: microangiopathy of the alveolar capillaries and pulmonary arterioles,⁵⁻⁸ chronic low-grade inflammation,^{9,10} autonomic neuropathy involving the respiratory muscles,¹¹ loss of elastic recoil secondary to collagen glycosylation of lung parenchyma, myopathy of respiratory muscles,¹² hypoxia induced insulin resistance¹³ and low birth weight associated with both insulin resistance and impaired lung function.¹⁴ Thus, diabetes leads to impairment of the alveolar capillary membrane and its consequences include the lengthening of the distance and time of gas exchange between interior of alveoli and erythrocytes in pulmonary capillaries. Thickening of the barrier results in decrease in oxygen saturation in erythrocyte (perfusion and diffusion). Loss of pulmonary elasticity and myopathy of respiratory muscles affects the ventilation. Thus all the three components are affected and contribute to lung dysfunction.¹¹

As the global burden of diabetes, obesity, smoking and heart failure is increasing, the significant additive negative effect on lung functions can result in increased morbidity and mortality associated with poor lung functions. Also, even if patients with diabetes exhibit subclinical pulmonary function abnormalities, in context of hypoxia associated with acute or chronic lung diseases or pulmonary edema, the loss of pulmonary reserve may become clinically important. Hence there is a need for assessing the pulmonary functions of type 2 diabetics and as a further guide for the periodic assessment of pulmonary functions. At present there is paucity of literature from Indian scenario and most of the studies are from urban settings. With this context, the present study was planned to assess the pulmonary functions by spirometry in patients of type 2 DM residing in rural areas in the hilly state of Himachal Pradesh.

METHODS

This was a case control study matched for age, sex, height and weight. Total 90 patients with type 2 DM were compared with 90 healthy controls from hospital. For diagnosis of DM, all cases and controls were assessed with the criteria laid down by Indian Council of Medical Research (ICMR); fasting blood glucose (FBG) ≥ 126 mg/dl and PPBG ≥ 200 mg/dl. Patients who were smoker, obese (Body mass index >30 kg/m²) suffering from cardiovascular disease and respiratory diseases were excluded from the study. During the data collection of there was an unacceptable spirometry technique which lead to incorrectly measured values because of cough, obstruction of tongue or teeth, sustained effort less than 6 seconds, recent surgery, failure to understand procedure, failure to attain plateau in volume-time graph was also excluded from the study. After informed consent, individuals were assessed for spirometry, height, and weight. The Body Mass Index (BMI) was calculated was calculated as weight in kilogram divided by height in metres square.³⁴ Spirometric test was performed using Spirolab III device. Subject was put in relaxed sitting position, with nose clip onto the nose to ensure that air did not escape through the nostrils. Mouth piece was put and when patient was ready, he was asked to inspire slowly as much air as possible. Then, without removing the mouth piece from the mouth he was asked to expire all of the air as fast as possible. Cycle was repeated three times and best of three acceptable manoeuvres were taken for interpretation. Following variables were assessed; FVC (Forced Vital Capacity), FEV1 (Forced Expiratory Volume at 1 second), PEF_{25-75%} (Peak Expiratory Flow Rate), and PEF (Peak Expiratory Flow). Subjects were assessed for obstructive and restrictive pattern of lung abnormality based on FEV1:FVC ratio and classified as ratio of $>70.0\%$ and $<70.0\%$, and again patients were assessed for classifying for predicted values of FEV1 is more or less than FVC. Patients with FEV1:FVC $<70.0\%$ were categorized as obstructive (along with FEV1 $<$ FVC) and $>70.0\%$ as restrictive pattern (along with FEV1 $>$ FVC) of lung abnormality. Thereafter, among diabetics correlation between age (years), gender (male and female), duration of diabetes (months), Body Mass Index (BMI in kg/m²), Waist Hip Ratio (WHR), FBS and PPBG for abnormal predicted lung function (cases with FEV1 and FVC difference) was assessed.

Interpretation of the test results was done by comparing the measured parameters with specific normal spirometry values (known as predicted values) which are calculated from subject data: age, height, weight, sex and ethnic group. After test session the results were compared to predicted values and the percentage ratio between measured and predicted was taken. Prior ethical approval was sought from Institute Ethics Committee (IEC). Data was entered and analyzed using Epiinfo.7 software. The continuous quantitative variables were analyzed using unpaired students't test and level of significance was reported.

RESULTS

A total number of 90 cases and 90 controls were recruited for the study purpose. The mean duration of diabetes in males was 87.6 ± 71 months and in females was 70.1 ± 71.1 months. Total 6 cases (3 males and 3 females) were newly diagnosed.

There were 39 males (43.4%) and 51 females (56.6%) in both study and control group. Overall, the mean age among cases and controls was 55.9 and 55.7 years respectively ($P = 0.90$).

The mean age of males in study group was 58.6 (range 35-78 years) and mean age of males in control group was 58.9 years (range 36-78 years). The mean age of females in study group was 53.8 (range 35-75 years) and mean age of females in control group was 53.3 year (range 35-75 years) (Table 1).

The mean weight and height of males in study group was 67.1 kg (range 48-87 kg) and 164.3 cm (range 154-185cm) and mean weight and height of males in control group was 67 kg (range 48-89 kg) and 165.2 cm (range 154-185 cm) respectively.

The mean weight and height among females in study group was 58.2 kg (27-76 kg) and 151.3 cm (range 139-169 cm) and among females in control group mean weight was 58.5 kg (range 30-76 kg) and mean height was 151.7cm (range 139-168 cm) (Data in table not shown).

The mean BMI of males in study group was 24.7 kg/m^2 (range $16.2\text{-}29.9 \text{ kg/m}^2$) and 24.8 kg/m^2 (range $16.3\text{-}29 \text{ kg/m}^2$) in control group ($P = 0.97$). Similar insignificant difference was observe among females with mean BMI of 25.5 kg/m^2 (range $13.7\text{-}29.9 \text{ kg/m}^2$) and 25.2 kg/m^2 (range $14.5\text{-}29.5 \text{ kg/m}^2$) respectively ($P = 0.67$) (Table 1).

In study group, the overall control of diabetes appeared to be poor in both males and females group. Despite on medication, the mean FBS (fasting blood sugar) and PPBS (post prandial blood sugar) were 158.87 mg/dl (range 76-345) and 233.67 mg/dl (range 138-486) in males respectively. As in males, among females, uncontrolled levels were observed for mean FBS and PPBS, 167.82 mg/dl (range 86-641) and 234 mg/dl (range 132-832) respectively.

The mean HbA_{1c} (glycosylated haemoglobin) level in males was 8.45% (range 6.6-12.7) and in females was 8.37 % (range 6.4-13.4). When assessed for complications, among diabetics, 63.3% (57; male=27: Female: 30) had neuropathy, 44.4% (40; male=22: Female: 18) had retinopathy, 41.1% (37; male=17: Female: 20) had nephropathy, 14.4% (13; male=5: Female: 8) had microalbuminuria. Overall, 63 (70%) of the patients had microvascular complications of diabetes in some form (Data not shown).

Table 1: Baseline and spirometric function analysis among cases (type 2 diabetes mellitus) and control (hospital healthy), 2012, Himachal Pradesh.

Characteristics	Cases (90)	Controls (90)	P value
Age (years)			
All	55.9	55.7	0.90
Male (39)	58.6	58.9	0.86
Female (51)	53.8	53.3	0.74
BMI (kg/m²)			
All	25.2	25.0	0.76
Male (39)	24.7	24.8	0.97
Female (51)	25.5	25.2	0.67
FBS (mg/dl)			
All	163.9	NA	NA
Male (39)	158.9	NA	NA
Female (51)	167.9	NA	NA
PPBS (mg/dl)			
All	233.9	NA	NA
Male (39)	233.7	NA	NA
Female (51)	234.1	NA	NA
FVC (liters)			
All	2.3	3.2	0.001
Male (39)	2.9	3.9	0.001
Female (51)	1.9	2.6	0.001
FEV1 (liters)			
All	2.06	2.64	0.001
Male (39)	2.5	3.2	0.001
Female (51)	1.7	2.2	0.001
FEV1:FVC			
All	88.6	82.2	0.001
Male (39)	86.1	82.7	0.08
Female (51)	90.5	81.8	0.001
PEFR_{25-75%} (liter/second)			
All	2.6	2.9	0.02
Male (39)	2.9	2.8	0.001
Female (51)	2.3	2.7	0.001
PEF (liter/sec)			
All	4.3	5.5	0.001
Male (39)	5.2	7.2	0.001
Female (51)	3.6	4.2	0.03

NA: As FBS and PPBS was not assessed among non-diabetics

When assessed for respiratory function, spirometry showed significant reduction among diabetics (both males and females) in all the parameters, except for FEV1/FVC in males (Table 1). When spirometric parameters were compared in cases with well controlled diabetes to that with uncontrolled diabetes, no significant differences were found (Table 2). When spirometric parameters were compared in cases with microvascular complications to that without complications, no significant differences were found. When assessed, it was observed that among cases (diabetics) males (56.4%) as compare to females (35.3%) were observed with

significantly ($P = 0.04$) more cases of retinopathy. Whereas, neuropathy was insignificantly ($P = 0.31$) different among males (69.2%) and female (58.8%) diabetics. Further, when retinopathy and neuropathy were

assessed for controlled (10) and uncontrolled diabetes (90), it was observed that in patients with uncontrolled diabetes, 47.5% of had retinopathy ($P = 0.09$) and 66.2% of patients with neuropathy ($P = 0.10$).

Table 2: Comparison of spirometric parameters between controlled and uncontrolled diabetics, 2012, Himachal Pradesh.

Variables (mean)	Males		P value	Females		P value
	HbA _{1C} <7 (n=6)	HbA _{1C} >7 (n= 33)		HbA _{1C} <7 (n=2)	HbA _{1C} >7 (n=49)	
FVC (liters)	2.62	2.94	0.28	1.9	2.0	0.95
FEV1 (liters)	2.19	2.53	0.20	1.8	1.7	0.86
FEV1:FVC	84.27	86.45	0.55	93.1	90.4	0.06
PEFR _{25-75%} (liter/second)	2.63	3.05	0.32	2.4	2.3	0.88
PEF (liter/sec)	5.25	5.20	0.95	3.7	3.6	0.91

Risk assessment for all 90 (100.0%) cases and 88 (97.7%) controls for lung dysfunction was assessed with FEV1:FVC ratio of $>70.0\%$ was done. This finding predicts for normal spirometry or restrictive pattern of lung impairment. OR for abnormal lung dysfunction among diabetics was 1.02 (CI: 0.99-1.05) as compare to non-diabetics. To delineate normal and restrictive pattern, patients with high level of predicted values of FEV1 as compare to FVC were assessed. It was observed that significantly ($p=0.00$) more (Cases:76.6%; Controls: 42.2%) cases had FEV1 $>$ FVC predicted levels as compare to controls, means among diabetics odds of restrictive pattern of lung abnormality is four times (OR: 4.4; CI: 2.3-8.5) more as compare to non-diabetics.

Among diabetics, in order to assess correlation of assessed variables with restrictive pattern of lung function (FEV1 $>$ FVC), it was found that age (Years) (r : 0.15), gender (r : 0.17) and duration of diabetes (months) were positively correlated but duration of diabetes was significantly (r : 0.39; $P = 0.00$) positively correlated. It meant that cases with more long standing diabetes mellitus were observed with more restrictive pattern of disease (FEV1 $>$ FVC). Other variables like BMI (r : -0.03; $P = 0.73$), WHR (r : -0.07; $P = 0.49$), FBS (r : -0.01; $P = 0.90$) were negative insignificantly correlated. PPBG was observed no correlation (r : 0.00; $P = 0.99$) with lung function.

DISCUSSION

This study was undertaken to assess the ventilatory functions of type 2 DM patients as compare to healthy controls. Few studies have been focussed on the relationship of pulmonary functions and diabetes. In this matched case control study, there were more of females in both groups due to exclusion of males for history of smoking. Matching was done for age, weight and height as these are major determinants of differential lung

function. The groups were also homogenous in respect of no respiratory disease and all being non-smokers. Present study observed mean age of 55.0 years as reported in other studies.¹⁵⁻¹⁸ Current study reported high prevalence of microvascular complications as 70%, 63.3% and 44.4% for neuropathy, retinopathy and nephropathy respectively. About 21.1% had only one complication, 17.7 % had two complications and 31.1% had all three microvascular complications. Neuropathy and retinopathy prevalence was observed similarly high in other study with low prevalence of nephropathy (12.7%).¹⁹ Compare to present study, other studies observed lower prevalence of neuropathy and retinopathy.²⁰⁻²² A review article on complications of diabetes in 2008 observed high rate of microvascular complications among Asians as compare to Europeans and Americans.²³ compared the prevalence of microvascular complications among Europeans, Americans and Asians. The complication rate depend upon duration and treatment compliance of DM, as in current study the mean duration of DM was about 6 years and only about 8.0% had good glycaemic control.

Overall, pulmonary function assessment showed that all spirometric values were significantly less ($P < 0.05$) for diabetics as compared to controls, so were for males (except for FEV1:FVC in males) and females. As expected, all spirometric values were lower for females as compared to males but there was no significant difference in degree of derangement and pattern of derangement of spirometric parameters between both sexes. All the parameters were significantly lower in diabetics than controls except FEV1/FVC which was higher among diabetic group. But the parameter was within normal range reflecting that both FEV1 and FVC were affected in DM and also relatively in same proportion so that ratio has not deviated from normal. Similarly, other studies showed low mean spirometric levels among diabetics than non-diabetics. Walter RE et al. (2003)²⁴ observed

FEV1 2.7L (± 0.77) vs. 2.92L (± 0.79) ($P < 0.001$), FVC 3.66L (± 0.98) vs. 3.95L (± 0.97) ($P < 0.001$) and FEV1/FVC 0.74 (± 0.07) vs. 0.74 (± 0.07) ($P = 0.71$); Verma S et al.¹⁸ observed FVC 2.12 ± 0.67 L vs. 2.45 ± 0.54 L ($P = 0.008$), FEV1 1.93 ± 0.53 L vs. 2.2 ± 0.49 L ($P = 0.008$) and FEV1/FVC $90.96 \pm 9.36\%$ vs. $90.19 \pm 5.86\%$; and Dharwadkar et al.²⁵ found FEV1 1.16 ± 0.49 L vs. 1.68 ± 0.46 L ($P < 0.001$), FVC 1.7 ± 0.66 L vs. 1.87 ± 0.57 L ($P = 0.33$), FEV1/FVC $67.44 \pm 16.51\%$ vs. $90.94 \pm 8.19\%$ ($P < 0.001$) in diabetics compared with nondiabetics. Simultaneously, there are were studies which showed insignificant difference for spirometric PFTs between patients with diabetes and normal control subjects.^{26,27} These inconsistencies may be due to the differences in population studied in terms of race, age group, and smoking history, variation in duration and metabolic control of diabetes and variation in measurement techniques.

Among the spirometric measures FVC is a measure of lung volume, FEV1 is a measure of patency of large airways and FEF_{25-75%} is a measure of patency of small airways. In the present study all the parameters found to be affected among diabetics suggested mixed ventilatory dysfunction. Studies observed restrictive pattern of lung function among diabetics.^{9,18,28} As in present study, Dharwadkar et al.²⁵ observed mixed ventilator dysfunction. The decreased lung volumes suggest restrictive ventilatory defect and decreased flow rates for small airways suggest early obstructive ventilatory defect. The proposed hypothesis for lung mechanical dysfunction in diabetes emphasizes the key role of advanced AGEs. There are supposed to be two mechanisms by which AGEs cause lung dysfunction in diabetes. The first mechanism that is proinflammatory effect of AGEs suggests obstructive lung mechanical dysfunction in diabetes. The second mechanism that is AGEs induced functional alterations in connective tissue of lung suggests restrictive lung mechanical dysfunction in diabetes. Hence, the pattern of spirometric dysfunction that is mixed ventilatory dysfunction observed in our study is consistent with proposed mechanisms for lung mechanical dysfunction in diabetes.

We compared the siprometric values in diabetic group between the patients with controlled and uncontrolled diabetes and observed no statistically significant difference between two groups though values among the uncontrolled group were lower than the controlled group. This observation was not in accordance to other studies. But this has to be interpreted with caution as there was considerable difference in the number of patients in each group. Yeh et al. (2008)²⁹ found FVC (% predicted): 2.9 vs. 3.8 vs. 4.2 lower in FBG < 140 vs. $140-199$ vs. > 200 mg/dl, respectively and FEV1 (% predicted): 2.3 vs. 2.6 vs. 2.4 lower in FBG < 140 vs. $140-199$ vs. > 200 mg/dl, respectively. But this decrease was not statistically significant. In Fremantle diabetes study²⁸ absolute measures continued to decline at an annual rate of 68, 71, and 84 ml/year and 17 l/min for FVC, FEV1, VC, and

PEF, respectively among the 125 prospectively studied patients. Declining lung function parameters were consistently predicted by poor glycaemic control in the form of a higher updated mean HbA_{1c}, follow-up HbA_{1c}, or follow-up fasting plasma glucose. Dharwardkar AR et al. (2011)²⁵ showed respiratory parameters FEV1, FEV1% are significantly but negatively correlated with FBS, & PPBS ($r = -0.39, -0.399, -0.326, -0.322$). Sharma B et al. (2003) observed HbA_{1c} levels are correlated significantly with FEV1, FEF_{25-75%}, PEFR, FVC and TLC ($p < 0.01$).

In our study we also compared the spirometric values in diabetes group between patients with microvascular complications to that without microvascular complications and observed no statistical significant difference which is consistent with other studies. Klein O et al.⁴ measured PEF during brief 1-2 seconds maximal forced expiratory efforts and found no association with progression of retinopathy, incidences of proliferative retinopathy, macular edema, lower extremity amputation or ulcer. Sinha et al.¹⁵ compared the PFTs in patient with complications and without complications and found FVC (% predicted) 80.4 ± 10.7 vs. 80.7 ± 15.8 ($P > 0.05$) and FEV1 (% predicted) 81.0 ± 9.4 vs. 80.1 ± 16.2 ($P > 0.05$) PEFR (% predicted) 83.3 ± 18.2 vs. 84.1 ± 25.3 ($P > 0.05$) DLco (cc/min/mmHg) 15.8 ± 3.1 vs. 17.5 ± 2.1 ($P < 0.001$). Aggrawal AS³⁰ found a significant reduction of diffusion capacity corrected for alveolar volume (%DL/VA) in group with complications ($p < 0.001$), as compared to the other groups but did not found significant difference among spirometry measures. There was a significant correlation between DL/VA percent predicted and albuminuria ($r = -0.975, P < 0.001$), and DL/VA percent predicted and the retinopathy ($r = -0.550, P < 0.05$). Boulbou et al. (2003)³¹ found no correlation between pulmonary function tests and diabetic complications. This may be because of the fact that lung dysfunction may start even before the presentation of diabetes suggesting that abnormal lung function may contribute to or at least be commonly affected by the factors involved in the pathogenesis of diabetes or the pathogenesis of both may involve same inflammatory pathways. This fact has been speculated in study by Davis et al (2004)²⁸ also. But Makkar P et al.³² in his study found diabetic patients with complications particularly peripheral neuropathy and nephropathy had significant reduction in FVC, FEV1 and PEF ($P = 0.001$).

Microvascular complications in lung parenchyma bring parenchyma changes and tend to report as restrictive pattern of lung dysfunction. Present study brought showed evidence that patients with DM presented with restrictive pattern of lung dysfunction due to fibrotic process, as reported by earlier evidences.^{33,34} Recent epidemiological studies and systematic reviews clearly indicate that DM as an independent risk factor for pulmonary dysfunction.³⁵ Histopathological findings in a study reported pulmonary fibrosis among type-1 diabetic patients with significant reduction in pulmonary

function parameters.³³ Such microvasculature changes in the form of tissue fibrosis not only observed in lung parenchyma but also in heart myocardium as well, evidence mentioned that such myocardial fibrosis, cardiomyocyte hypertrophy and altered microvasculature was resulted due to DM.³⁶ For such fibrotic process Angiotensin II plays an important factor for diabetic lung fibrosis resulted due to NOX activation-mediated nitrosative damage.³⁵

Thus, our study has demonstrated clear cut negative effect on mechanical lung function in diabetic subjects suggesting lung as a target organ, but could not establish its relationship to the glycaemic control and the other microvascular complications. Although there is significant derangement of spirometric functions in diabetic patients, this dysfunction is not severe enough to be clinically significant. In other words, we can say that diabetic subjects have subclinical mechanical lung dysfunction. This subclinical loss in pulmonary reserve may become clinically important in context of hypoxia induced by superimposed acute or chronic lung disease, cardiac disease or renal failure which are common complications of diabetes and can add up significantly to the morbidity and mortality. This may also lower the threshold for clinical manifestation of other respiratory diseases.

Our study has limitation. We have not checked the DLco (Diffusing capacity of Lungs) in our patients. Several studies showed that DLco is significantly reduced in diabetic patients, even in patients with normal spirometry. This poses a methodological limitation in the current study.

Based on the findings of current study in the context of growing literature, it can be concluded that spirometric lung dysfunction does not correlate with control of diabetes and microvascular complications of diabetes and it can be used routinely to assess the subclinical pulmonary dysfunction in type 2 DM patients.

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