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A Case Control Study: To Correlate Lung Functions with Microvascular Complications in Patients with Diabetes and Normal Individuals

Bhavya. R*, [1]Dhruthi G, [2] Chekuri S.N.V.S.K.N. Ravi Varma

*Assistant Professor, Department of Nephrology, Rajarajeswari Medical College and Hospital, Bangalore., India

[1]Junior Resident, Department of General Medicine, Rajarajeswari Medical College and Hospital, Bangalore., India

[2]Chekuri S.N.V.S.K.N. Ravi Varma, Junior Resident, Department of General Medicine, Rajarajeswari Medical College and Hospital, Bangalore., India

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ABSTRACT

Background and objective: With its fast-rising prevalence, diabetes is a global health concern. Both macrovascular and microvascular problems have been reported to be accelerated by it. Research on the relationship between diabetes and pulmonary function has been inconsistent. Reduced lung function in patients with Type 2 diabetes mellitus may be linked to longer illness duration and microangiopathy indicators. This study aimed to assess the lung functions of patients with type 2 diabetes mellitus in comparison to age- and sex-matched normal individuals, and to establish a correlation between the existence of microvascular problems and the spirometric results. **Method:** A cross-sectional comparative study with a hospital setting was carried out during a 1.5-year period. The subjects were divided into two groups: sixty healthy volunteers and sixty T2DM patients who were selected at random from both the in-patient and out-patient departments. A detailed history, clinical examination and microvascular complications details entered in a structured proforma. In both groups, a pulmonary function test was conducted. **Results:** This study included 60 age- and sex-matched cases and 60 healthy participants (controls) who met the inclusion criteria. Among 60 cases, 24 had microvascular complications and 36 had no microvascular complications. Of 24 subjects with microvascular complications 6 (25%) had normal pulmonary function and 18 (75%) had restrictive pattern of pulmonary function. Of 36 subjects without microvascular complications 22 (61.1%) had normal pulmonary function and 14 (38.9%) had restrictive pattern of pulmonary function. There was a significant difference in pulmonary function in subjects with microvascular complication (P value 0.006). Restrictive pattern of pulmonary function was more in subjects with microvascular complications. **Conclusion:** This study revealed that patients with diabetes had reduced lung function, primarily in a restrictive pattern. As diabetes duration increased and the risk of microvascular complications present, pulmonary dysfunction grew worse. Lung dysfunction was statistically significantly correlated with other microvascular injury indices.

Keywords: Lung Functions, Microvascular Complications, Diabetes

INTRODUCTION

Diabetes mellitus is the most prevalent non communicable and metabolic disorder in the world and characterized by hyperglycemia resulting from defects in insulin secretion, action or both. It is a big concern because of the devastating effect of its chronic complications.

Diabetes mellitus is a risk factor which precipitates micro vascular pathologies leading to autonomic neuropathy, nephropathy, retinopathy, peripheral neuropathy and macro vascular pathologies leading to coronary artery disease, cerebrovascular accidents and peripheral vascular disease. The micro vascular complications appear early, within 5 to 10yrs and macro vascular complications appear within 15 to 20yrs from the onset of diabetes. If diabetes mellitus is detected early and adequate steps are taken, it is possible to significantly delay the occurrence of complications and thereafter the progression.[1]

There are histopathological changes seen in lungs of subjects with diabetes mellitus such as thickened alveolar epithelial cells and pulmonary capillary basal lamina leading to reduced pulmonary elastic recoiling of lung tissue. There is impaired diffusion of gases due to reduced pulmonary capillary blood volume and thickening of the basement membrane. Non-enzymatic glycosylation induced alteration of lung connective tissue is the most likely mechanism underlying the

mechanical pulmonary dysfunction in Type-2 DM patients. This suggests that the lung is one of the 'target organs' in diabetes mellitus.[2]

The review of research work in this field shows the involvement of respiratory system in Type 2 DM. The pulmonary functions in diabetes mellitus are not so extensively documented. The present study is undertaken to evaluate the impact of Type 2 DM on pulmonary functions and compare the results of pulmonary function tests in patients with Type 2 DM and normal individuals.

MATERIALS AND METHOD

STUDY DESIGN: Case-control study.

STUDY DURATION: 1.5 Years.

STUDY SETTING: Case control study for 1.5 years at Tertiary Care Centre

SAMPLE SIZE:

- Cases – 60
- Controls – 60

STUDY POPULATION:

Study population will be divided into 2 groups

- Group A (case) consists of all patients with type 2 DM attending the in-patient and outpatient department.
- Group B (control) consists of normal individuals.

According to WHO diagnostic criteria for diabetes is:

- Symptoms of diabetes with random blood sugar - ≥200mg/dl or
- Fasting plasma glucose - ≥126mg/dl (7.0mmol/l) or
- 2-hour plasma glucose value after a 75g OGTT - ≥200mg/dl (11.1mmol/l) or
- HbA1c > 6.5%.

INCLUSION CRITERIA: Type 2 Diabetes mellitus patients

EXCLUSION CRITERIA:

- Smokers
- Present or past history of respiratory diseases that might affect lung function such as asthma, COPD, tuberculosis, bronchiectasis, interstitial lung disease.
- History of occupational exposure to any substances that could affect lung function.
- Individuals with current or recent upper respiratory or lower respiratory infection, that could pre-dispose to heightened airway reactivity.
- History of ischemic heart disease in the past.
- T2DM patients with macrovascular complications.

METHOD OF COLLECTION OF DATA:

Subjects included in the study recruited from both in-patient and out-patient departments were requested to attend a medical interview and undergo physical examination including fundoscopy.

Non-smoking type 2 DM patients with no history of respiratory disease, and who give informed consent were selected for this study and underwent pulmonary function testing.

Healthy, non-smoking, normal individuals were chosen as controls, to undergo pulmonary function testing.

STATISTICAL ANALYSIS:

- Pulmonary function tests of patients with type 2 diabetes mellitus and controls were compared by applying Student′s unpaired ′t′ test.
- The correlation between microvascular complications and pulmonary function test was analyzed by applying chi square test.
- Statistical analysis was done by using SPSS version 20.

RESULTS

Table 1: Comparison of Pulmonary function test in type 2 diabetes patients and normal subjects

		Cases (%)	Control (%)	Chi square	P value
PFT	Normal	36 (60)	50 (83.33)	8.044	0.005*
	Restrictive Pattern	24 (40)	10 (16.67)		

(* indicates significant at the 5% level of significance)

Since the Chi square P value is less than 0.05 there was a difference in pulmonary functions among the subjects.

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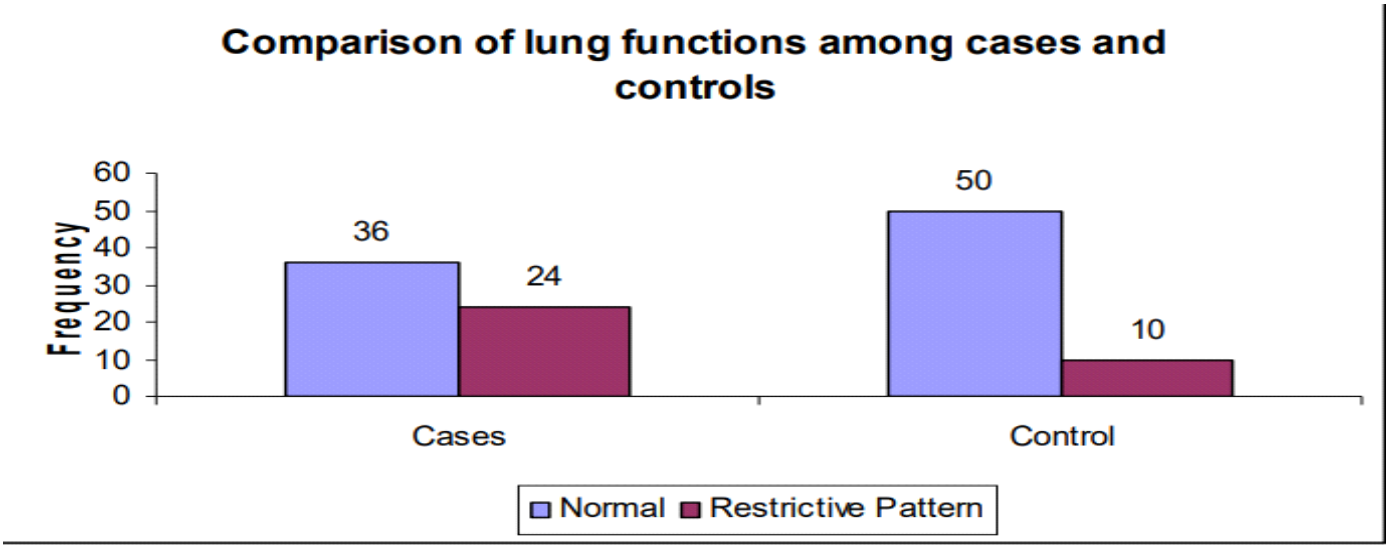

Figure 1: Comparison of lung functions among cases and controls

Table 2: Correlation between microvascular complications and Pulmonary Function Test

		Normal PFT (%)	Restrictive Pattern (%)	Chi square	P value
Microvascular complications	Absent	22 (61.1)	14 (38.9)	7.545	0.006*
	Present	6 (25)	18 (75)		

(* indicates significant at the 5% level of significance)

Since the Chi square P value is less than 0.05 there was a difference in pulmonary functions among subjects with microvascular complications and those without microvascular complications.

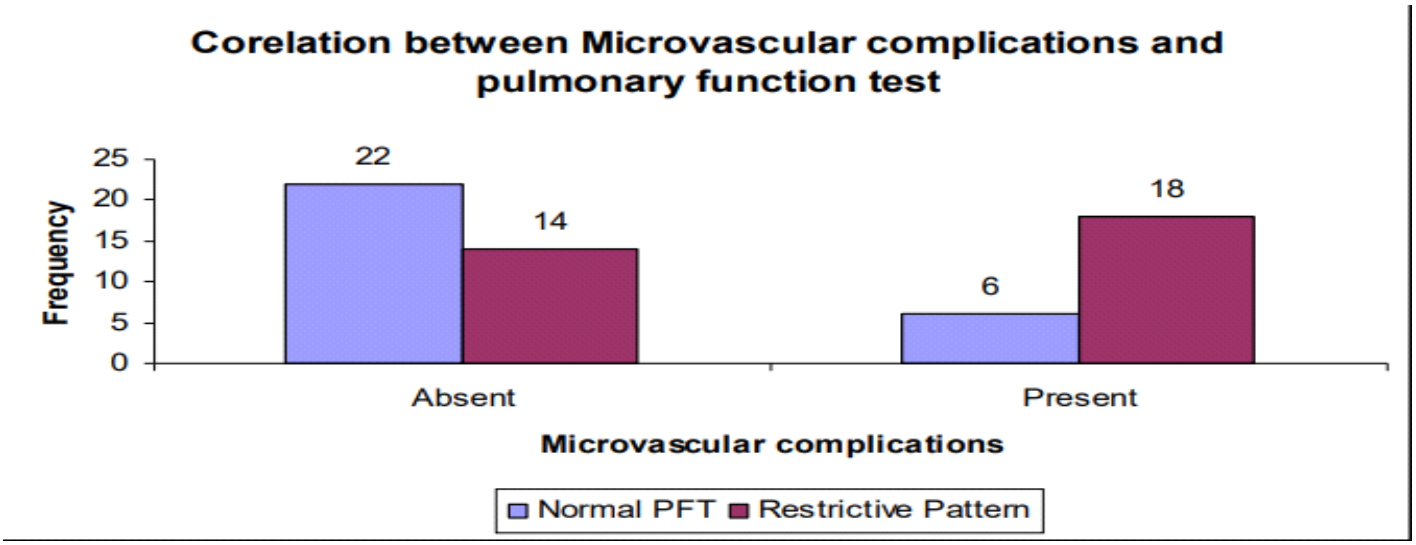

Figure 2: Correlation between microvascular complications and Pulmonary Function Test

Among 60 cases, 24 had microvascular complications and 36 had no microvascular complications. Of 24 subjects with microvascular complications 6 (25%) had normal pulmonary function and 18 (75%) had restrictive pattern of pulmonary

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function. Of 36 subjects without microvascular complications 22 (61.1%) had normal pulmonary function and 14 (38.9%) had restrictive pattern of pulmonary function. There was a significant difference in pulmonary function in subjects with microvascular complication (P value 0.006). Restrictive pattern of pulmonary function was more in subjects with microvascular complications.

Table 3: Correlation between nephropathy and pulmonary function in subjects with T2DM

		Normal PFT	Restrictive Pattern	Chi Square	P value
Nephropathy	Absent (%)	26(70.27)	11(29.73)	4.242	0.039*
	Present (%)	10(43.48)	13(56.52)		

(* indicates significant at the 5% level of significance)

Since the Chi square P value is less than 0.05 there was a difference in pulmonary functions among subjects with nephropathy and those without nephropathy.

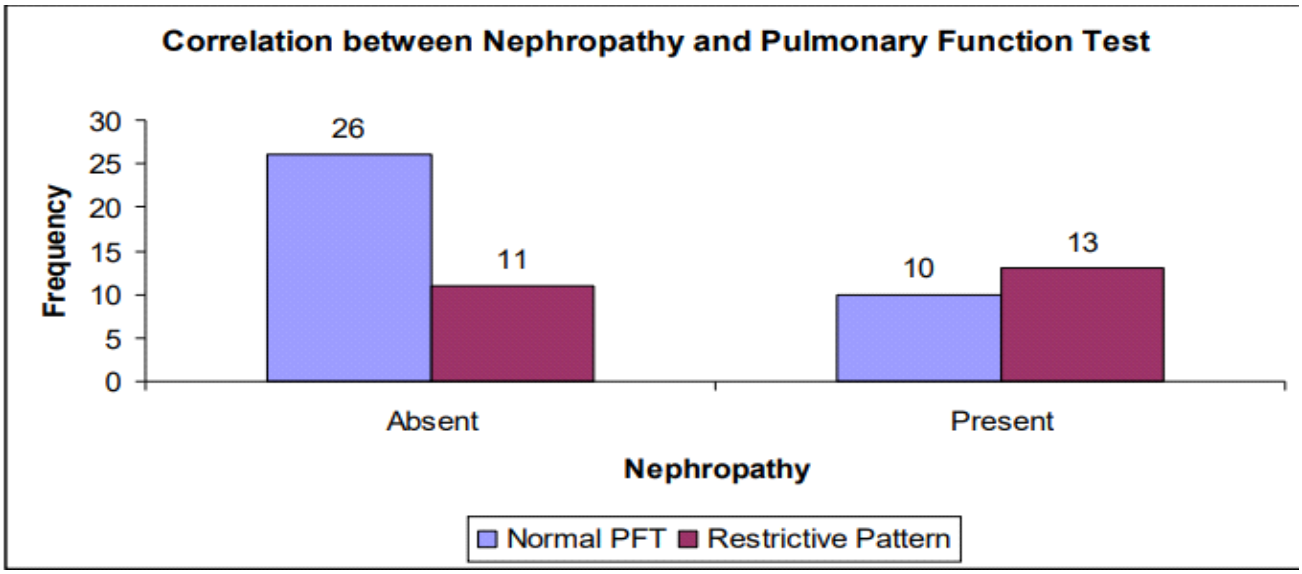

Figure 3: Correlation between nephropathy and pulmonary function in subjects with T2DM

Among total 60 cases, 23 had nephropathy and 37 did not have nephropathy. Of the 23 subjects with nephropathy 13(56.52%) had restrictive pattern of pulmonary function. Of the 37 subjects without nephropathy 11(29.73%) had restrictive pattern of pulmonary function. Restrictive pattern of pulmonary function was higher in patients with nephropathy which was statistically significant (P value 0.039).

Table 4: Correlation between retinopathy and pulmonary function in subjects with T2DM

		Normal	Restrictive Pattern	Chi square	P value
Retinopathy	Absent (%)	27(75)	9(25)	8.438	0.004*
	Present (%)	9(37.5)	15(62.5)		

(* indicates significant at the 5% level of significance)

Since the Chi square P value is less than 0.05 there was a difference in pulmonary functions among subjects with retinopathy and those without retinopathy.

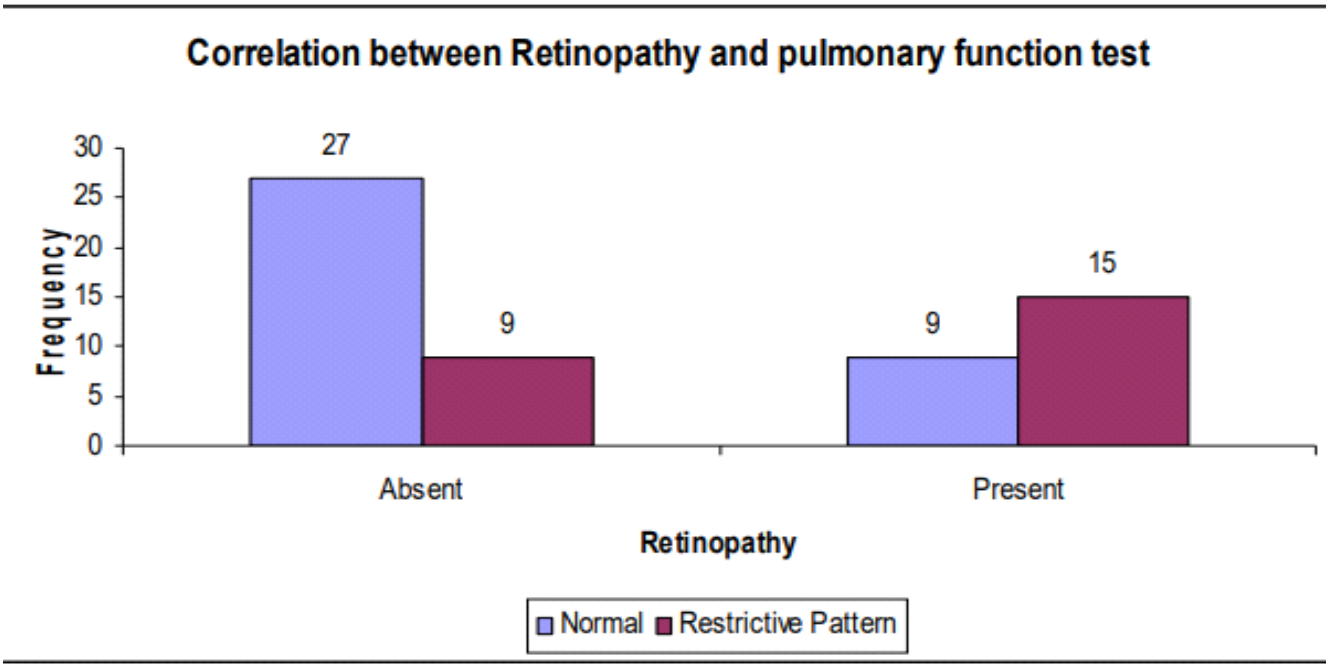

Figure 4: Correlation between retinopathy and pulmonary function in subjects with T2DM

Among total 60 cases, 24 had retinopathy and 36 did not have retinopathy. Of the 24 subjects with retinopathy 15(62.5%) had restrictive pattern of pulmonary function. Of the 36 subjects without retinopathy 9(25%) had restrictive pattern of pulmonary function. Restrictive pattern of pulmonary function was higher patients with retinopathy which was statistically significant (P value 0.004).

Table 5: Correlation between neuropathy and pulmonary function in subjects with T2DM

		Normal	Restrictive Pattern	Chi Square	P value
Neuropathy	Absent (%)	35(70)	15(30)	10.125	0.001*
	Present (%)	1(10)	9(90)		

(* indicates significant at the 5% level of significance)

Since the Chi square P value is less than 0.05 there was a difference in pulmonary functions among subjects with neuropathy and those without neuropathy.

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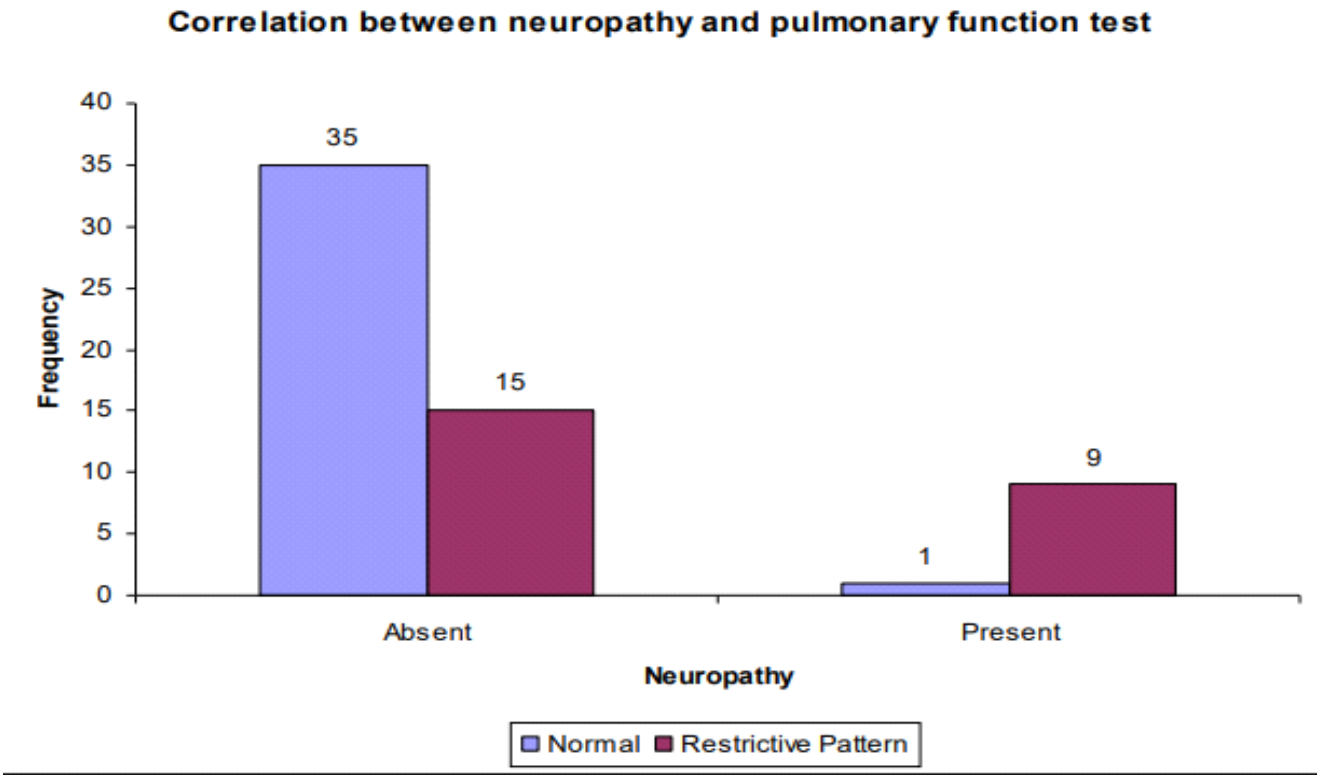

Figure 5: Correlation between neuropathy and pulmonary function in subjects with T2DM

Among total 60 cases, 10 had neuropathy and 50 did not have neuropathy. Of the 10 subjects with neuropathy 9(90%) had restrictive pattern of pulmonary function. Of the 50 subjects without neuropathy 15(30%) had restrictive pattern of pulmonary function. Restrictive pattern of pulmonary function was higher in patients with neuropathy which was statistically significant (P value 0.001).

DISCUSSION

DIABETES AND LUNG FUNCTION:

Study conducted by ***Yeh et al.*** included 1,100 individuals with diabetes and 10,162 individuals without diabetes from the Atherosclerosis Risk in Communities Study, showed that adults with diabetes had lower predicted levels of FVC and FEV1 when compared to those without diabetes with P value of <0.001. This result was found to be significant after adjusting for 50 demographic characteristics, smoking, adiposity and physical activity index. They found that increased duration of diabetes, higher blood sugars, diabetes severity based on antidiabetic medications were associated with lower predicted FVC and FEV1 levels (P <0.001). Prospective analysis of these subjects after 3 years showed faster decline in level of FVC in subjects with diabetes when compared to those subjects without diabetes. The rate of decline was 64ml/year in members with DM when compared to 58ml/year in members without DM (P = 0.01). [3]

Gregory et al studied pulmonary functions among participants with >10 pack year history of smoking with and without history of COPD and compared among subjects with and without diabetes. COPD Gene study included 10,129 participants and measured pulmonary function, exercise capacity, and pulmonary-related quality of life. Participants with diabetes were observed to have reduced pulmonary function after controlling for known risk factors and significant reductions in exercise capacity and quality of life. FVC was significantly lower in subjects with diabetes overall (P < 0.0001). Both FEV1% and FVC% were significantly reduced overall in subjects with DM (P = 0.03) and (P < 0.001). FEV1/FVC ratio was increased in subjects with diabetes overall; statistically significant increase in FEV1/FVC ratio was observed among GOLD 2 and 3 subjects but not among other COPD groups. They found that diabetes was associated with decreased lung function in current and former smokers with >10 pack-year history of smoking who do not have obstructive lung disease.[4]

Restrictive pattern of pulmonary function was observed in Indian study conducted by ***Swathi et al.*** It was a case control cross sectional study. There was significant reduction in all spirometric indices except FEV1/FVC, in subjects with T2DM when compared to their normal counterparts. [5] A study conducted in Japan by ***Asanuma et al.*** also reported reduction of both FVC and FEV1 in individuals with DM compared to nondiabetic subjects.[6]

In this study, patients with T2DM had a higher prevalence of restrictive pattern of lung dysfunction. 24(60%) out of 60 cases had restrictive pattern while 10(16.67%) out of 60 controls had restrictive pattern on PFT. Subjects with T2DM

had higher prevalence of lung dysfunction when compared to their normal counterparts which was statistically significant with a P value of 0.005. Results are consistent with previous studies. Most of the subjects with abnormal lung function had mild restrictive lung dysfunction. Among the 24 cases; 10(41.68%) had mild restrictive pattern, 6(25%) cases had moderate restrictive pattern, 4(16.66%) had moderately severe and 4(16.6%) had severe restrictive pattern. The mean percentage predicted FVC in subjects with T2DM was 80.13, found to be lower than their non-diabetic counterparts who had a mean percentage predicted FVC of 90.52. The difference was statistically significant with a P value of 0.008. Mean percentage predicted values of FEV1 were also lower (90.40) in individuals with T2DM when compared their nondiabetic counterparts who had mean percentage predicted FEV1 of 96.95. However, FEV1 reduction in this study was not statistically significant (P value 0.059). The FEV1/FVC ratio tended to be higher in subjects with T2DM although this was not statistically significant at the 0.05% level.

DURATION OF DIABETES AND LUNG FUNCTION:

Wendy et al. conducted a prospective study among 125 patients with diabetes. They were followed up for a period of 7.0 ± 0.5 years. FVC, FEV1, VC and PEFR were measured at baseline and follow-up. All four values decreased significantly. The mean rate of decrease was 71 ml/year (1.5% predicted/year) for FEV1, 68 ml/year (1.1% predicted/year) for FVC, 84 ml/year (1.6% predicted/year) for VC, and 17 l/min per year (3.1% predicted/year) for PEFR (P value <0.001 in each case). This was the largest study to have examined prospectively the relationship between diabetes and pulmonary function. FVC and FEV1 decreased by means of 68 and 71 ml/year in absolute terms. The rate of reduction in spirometric values in general population was ≤40 ml/year. There was a statistically significant reduction in lung function with increased duration of diabetes (P value <0.001). [7]

Current study also shows significant association between the percentage predicted values of the various spirometric indices and the duration of diabetes. FVC showed significant negative correlation with duration of diabetes (r= -0.44, P=<0.001), FEV1 also showed negative correlation with duration of diabetes (r= -0.425, P=0.001) while FEV1/FVC showed a positive correlation which was not statistically significant (r=0.048, P=0.713).The results obtained in our study are consistent with the previous studies. The median duration of diabetes was 36 months among cases with normal lung function, while the median duration of diabetes was found to be 72 months in diabetic patients who had lung dysfunction. This difference was statistically significant with a P value of 0.016.

MICROVASCULAR COMPLICATIONS AMONG PATIENTS WITH DAIBETES AND LUNG FUNCTION:

Microangiopathy specifically affects eyes causing retinopathy, kidney causing nephropathy and peripheral nervous system causing neuropathy. There is little known about the influence of diabetic microangiopathy affecting lung function. There are a few studies describing lung function and DLCO impairment in patients with both T1DM and T2DM.

The alveolar-capillary barrier damage is assessed by decreased DLCO. However, due to practical limitations it is difficult to assess DLCO in general population.

The current study suggests the presence of a preexisting microvascular complication may contribute to the development of lung dysfunction, especially in DM patients. Thus, microangiopathic changes of the lungs in patients with diabetes may be associated with other microvascular complications. There is variable data regarding this association. Hence further studies are needed to confirm the association between diabetic microangiopathy and lung dysfunction.[8]

Harris et al. studied whether microvascular changes in the retina and kidneys were associated with abnormal spirometry and low lung density on computed tomography. 3,397 participants were included in the study. They observed that retinal venular calibre was inversely associated with FEV1 and FEV1/FVC ratio. Nephropathy was inversely associated with FEV1 and FVC but not FEV1/FVC. Pulmonary dysfunction was associated with microvascular changes in eyes and kidneys. This study suggests that the microvascular damage with end-organ dysfunction affects lungs as it affects other organs such as eyes and kidneys.[9]

Sinhala et al. conducted a study among Asian Indian population. They studied pulmonary functions in T2DM patients and correlated with microvascular complications. 29 patients with T2DM and 11 healthy controls were included in the study. They were divided into three groups. Group one included those with microangiopathy (retinopathy, nephropathy or neuropathy; n=12), group two included patients with T2DM without any complications (n=17), group three included healthy controls (n=11). There was significant reduction in 56 DLCO in group 1 (P<0.001), when compared to the other groups. However, other parameters such as forced vital capacity, forced expired volume in one second, peak expiratory flow rate, and maximal static inspiratory and expiratory pressures did not show difference between the three groups. There was significant correlation between pulmonary function and nephropathy (r=0.42, P<0.05). There was positive correlation between renal dysfunction and lung volumes. The lung volumes such as FVC and FEV1 positively correlated with the eGFR, strongest correlation was with the association between FEV1 and eGFR (r= 0.508, p=0.064). [10]

Shafiee et al. studied the association between pulmonary function and diabetic nephropathy in patients with T2DM. They reported that the percentage predicted FEV1, FVC and PEFR were significantly lower in subjects with renal impairment compared to healthy controls. Among those patients with T2DM, FVC and FEV1 were lower in those

with diabetic nephropathy compared to those without nephropathy (P<0.05). FEV1/FVC was significantly higher in subjects with diabetic nephropathy.[11]

The result from this study shows that among 60 cases, 24(40%) had microvascular complications. Among 24 patients with microvascular complications 18 (75%) subjects had restrictive pattern of lung dysfunction. Among 36 subjects without microvascular complications 22(61.1%) had normal pulmonary function and 14(38.9%) had restrictive pattern of pulmonary function. Patients with microvascular complications showed restrictive pattern of lung function which was statistically significant with a P value of 0.006. Results of this study are consistent with other studies and higher incidence of lung dysfunction was observed in patients with microvascular complications.

On comparing results individually, total subjects with nephropathy were 23, of which 13(56.52%) had restrictive pattern of pulmonary function. Among 37 subjects without nephropathy 11(29.73%) had restrictive pattern of pulmonary function. The difference in pulmonary function among subjects with nephropathy and those without nephropathy was statistically significant with a P value of 0.039. Among 24 patients with diabetic retinopathy, 15(62.5%) showed restrictive pattern of lung function. Of the 36 subjects without retinopathy, only 9(25%) had restrictive pattern of lung function. Restrictive pattern of pulmonary function was found to be higher among patients with retinopathy which was statistically significant with a P value 0.004. Among 10 patients with diabetic neuropathy, 9(90%) had restrictive pattern of lung function. Among those without diabetic neuropathy, 15(30%) had restrictive pattern of pulmonary function. Incidence of restrictive lung dysfunction was higher in those with diabetic neuropathy which was statistically significant (P value 0.001). Results of this study show that lung could be another target organ of diabetes.

Limitations of the study:

- Small sample size
- A longitudinal study over a longer period would better detect the effect of diabetes on pulmonary function.

CONCLUSION

A total of 120 patients were included in the study, 60 were cases and 60 were controls. Restrictive pattern of lung function was seen in 40% of the cases and in 16.67% of the control. There was a significant statistical difference between cases and controls (P value–0.005). The mean value of FVC and FEV1 was lesser among cases when compared to controls which was statistically significant. There was statistically significant correlation between duration of diabetes and abnormal pulmonary function test (P value–0.016). Median duration of diabetes among patients with normal lung function was 36 months while in those with abnormal lung function median duration of diabetes was 72 months. Among 24 subjects with microvascular complications 75% of them had restrictive pattern of lung function. This correlation between microvascular complications and lung dysfunction was statistically significant (P value-0.006). This study also found higher incidence of lung dysfunction among subjects with retinopathy, nephropathy and neuropathy which was statistically significant. Results from our study are consistent with growing body of evidence that diabetes may affect lung leading to restrictive pattern of lung dysfunction.

This study showed impaired lung function predominantly restrictive pattern in patients with diabetes. Results are like other larger studies. It is important to study lung function in patients with diabetes as impaired lung function may lower the threshold for acute or chronic lung diseases among subjects with diabetes. Pulmonary dysfunction worsened with increase in duration of diabetes. There was statistically significant association between lung dysfunction and other indices of microvascular injury. Further prospective studies are needed to confirm this observation and to establish lung dysfunction as a marker of microvascular complication.

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