Original Article

Frequency Of Restrictive Pulmonary Dysfunction In Type-1 & Type-2 Diabetes Mellitus

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Objective: To determine the frequency of restrictive pulmonary dysfunction in type 1 & type 2 diabetic patients and to measure the severity of pulmonary dysfunction.

Material & Methods: This study included 255 patients of type I and type II diabetes who had followed up in the out patient departments of Pulmonology and Medicine in Mayo Hospital, Lahore. Forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1) were measured using standard spirometry.

Results: Mean age was 47.26±19.076 years. 230 (90.2%) were males and 25 (9.8%) were females. 58 (22.7%) were type 1 diabetics and 197 (77.3%) were type 2 diabetics. 37 (14.5%) had restrictive pathology, 6 (2.4%) had obstructive pathology and 212 (83.1%) had normal lung function tests. 35 (13.7%) had mild restrictive dysfunction and 2 (0.8%) had moderate restrictive lung dysfunction.

Conclusion: These data support the notion that the lung is a target organ for diabetic injury. Additional research is required to identify pathophysiologic mechanisms and to determine clinical significance.

Keywords: Diabetes Mellitus, Pulmonary function tests, Restrictive lung disease

Introduction

Diabetes mellitus is a heterogeneous group of disorders characterized by variable degree of insulin resistance, impaired insulin secretion and increased insulin production. The worldwide prevalence of DM has risen dramatically over past two decades. In 2000 it was 0.19 percent in people less than 20 years old and 8.6 percent in people more than 20 years; in individuals more than 65 years, it was 20.1 percent.[1]

Diabetes Mellitus causes decrease in gas exchange and reduction in lung volume. The Frementle Diabetes Study showed that in type-2 diabetes mellitus (DM 2), decline in lung function is at an annual rate of 68, 71 and 84 ml per year for FVC, FEV1 and VC, respectively as compared to 25 to 30 ml per year in non smoker and non diabetic healthy individuals. This declining lung function is related to poor glycemic control.[2] Diabetes was associated with reduced lung function in 20.5% of 421 subjects with type-2 diabetes.[3] The Copenhagen City Heart Study carried out in 266 individuals with diabetes mellitus showed that FEV1 and FVC were consistently lower in diabetic individuals, compared with healthy individuals with an average reduction of 8% of predicted value.[4] Lung function in DM 2 is impaired by decrease in FEV1, FVC and PEF, as compared to their matched controls. Stratification of results by year of disease showed a dose response effect on lung function.[5]

Reduced lung function is also seen in type-1 diabetes mellitus. A study was done on 22 young type-1 diabetes patients. The percentage of patients showing reduced lung function was 45%.[6] The data indicates that type-1 diabetes patients showed reduced TLC and DLco, a feature of pulmonary restrictive dysfunction.[7]

In DM, lung function can be an important marker of increased risk of morbidity and mortality. This study was conducted to determine the effect of diabetes on pulmonary function.

Objective

The objective of this study was to determine the frequency of restrictive pulmonary dysfunction in type 1 & type 2 diabetes and to measure the severity of pulmonary dysfunction.

Operational Definitions

Forced Vital Capacity (FVC): FVC is the maximum volume of air exhaled with maximum forced effort from a maximal inspiration. FVC is expressed in liters.

Forced Expiratory Volume in One Second (FEV1): FEV1 is the maximum volume of air exhaled in the first second of a forced expiration from a position of full inspiration. It is expressed as liters.

FEV1/FVC Ratio (FEV1%): It indicates what percentage of total FVC was expelled from the lungs during the first second of forced exhalation. The normal ratio is 75-85%.

Restrictive vs Obstructive Pathology: Subjects in the study were classified according to the algorithms proposed by ATS/ERS.[8] A patient with an FVC less than the LLN and an FEV1/FVC ratio above the LLN (RPLLN) was categorized as having RP. Operationally restrictive lung dysfunction is defined as having increased FEV1/FVC ratio from its normal predictive value. It depends upon value of FVC.

A patient with an FEV1/FVC ratio less than the LLN was categorized as having OP.

Severity of Restrictive Lung Dysfunction: The severity of RP was assessed according to FVC percent predicted, as reported in the ATS/ERS guidelines.[9] Severity depends upon reduction of FVC from its normal predicted value as follows:

Normal: FVC ≥80% of predicted.

Mildly Impaired: FVC 60% To 79% of predicted.

Moderately Impaired: FVC 51% to 59% of predicted.

Severely Impaired: FVC 50% or less of the predicted.

Predicted Values Of Lung Function Tests: The prediction equations for normal lung function are as follows for men:

Predicted FVC = 0.042 x height - 0.024 x age - 1.785

Predicted FEV1/FVC = 0.028 x height - 0.19 x age - 89.313

Predicted FEV1 = 0.036 x height - 0.028 x age - 1.178

And For Women:

Predicted FVC = 0.031 x height - 0.019 x age - 1.105

Predicted FEV1/FVC = 0.09 x height - 0.249 x age - 111.052

Predicted FEV1 = 0.022 x height - 0.022 x age - 0.005

Diabetes Mellitus: Individuals were classified as having diabetes if any of the following criteria, adapted from American Diabetes Association criteria, were met: fasting glucose level of at least 7.0 mmol/l (126 mg/dl); non fasting glucose level of at least 11.1 mmol/l (200 mg/dl); current use of anti diabetes medication; or a positive response to the question "has a doctor ever told you that you had diabetes (sugar in the blood)?"

Material And Methods

Study Design: Descriptive study.

Setting: Study included OPD patients of the Pulmonology department and general medicine department at Mayo Hospital Lahore.

Sample Size: The calculated sample size was 255 with 5% margin of error, 95% confidence level, taking expected percentage of restrictive pulmonary dysfunction in type 2 diabetes mellitus as 20.5%.

Sampling Technique: Non-probability purposive sampling

Sample Selection

Inclusion Criteria

1- Diagnosed cases of type 1 and type 2 diabetes mellitus.
2- Duration of diabetes 5-10 years.
3- Non smokers
4- Patients of either sex
5- Age < 20 years in type 1 and > 30 years in type 2 diabetes mellitus.

Exclusion Criteria

1. Patients having any underlying lung disease or any pathology on chest x-ray.
2. Occupational exposure (farmers, miners, coal workers, carpenters, shipyard workers, plumbers, welders, sandblasters).
3. Patients of IHD, having infarction (MI) in last one month or evidence of congestive cardiac failure.

Data Collection Procedure: Patients with type 1 and type 2 diabetes mellitus, visiting medical and chest out door clinics of Mayo Hospital Lahore, were selected according to inclusion criteria in the study. Consent was taken in written form from subjects for undergoing pulmonary function tests. Procedure was explained practically. Risks and benefits were explained to the subjects. The demographic information of these subjects like name, age, sex, height and weight were recorded. Pulmonary function tests were performed by spirometery on Spirolab 11, results obtained and interpreted in terms of restrictive lung dysfunction and the severity measured. The test was performed in a standing position by trained technicians. All collected information was recorded on pre designed Performa.

The observed FVC was divided by the predicted FVC to yield %PFVC. FEV1 was divided by the observed FVC to yield the FEV1/FVC ratio, which is a continuous variable indirectly related to airway resistance. We quoted the standard predicted values for FVC, FEV1/FVC ratio, and FEV1 from data published by The Japanese Respiratory Society in 2001.[28]

Data Analysis Procedure: All data were entered into SPSS 17.0. The quantitative variables (age, height, weight and pulmonary function tests) were presented in the form of mean ± standard

deviation, Standard Error (SE) and range. The qualitative variables like sex, occupation and spirometery interpretation i.e. pulmonary restrictive dysfunction (yes / no) were presented in the form of frequency and percentage.

Results

Our study included 255 diabetic patients. The mean age was 47.26±19.076 years. 230 (90.2%) were males and 25 (9.8%) were females. The mean height was 153 ± 3.97 cm. 58 (22.7%) were type-1 diabetics and 197 (77.3%) were type 2 diabetics.

The mean FVC was 3.26± 0.55 L whereas the mean predicted FVC was 3.207±0.484 L. The mean percent predicted FVC was 96.2±15.22 and the LLN was 2.45±0.46 L.

The mean FEV1 was 2.98± 0.57 L whereas the mean predicted FEV1 was 2.59±0.44 L. The mean percent predicted FEV1 was 112.2±21.33 and the LLN was 1.935±0.49 L.

The mean FEV1/FVC% was 83.09±10.57 whereas the mean predicted FEV1/FVC% was 113.02 ±29.4. The mean percent predicted FEV1/FVC% was 112.2±21.33 and the LLN was 75.55±1.35L.

Table-1: Summary of Spirometry results.

	Mean	Std. Deviation
FVC L	3.26	.5517
FEV1 L	2.89	.5742
FEV1/FVC ratio	88.68	5.883
FVC, predicted	3.207	.4849
FVC%, predicted	96.22%	15.229
FVC, LLN	2.45	.4659
FEV1, predicted	2.59	.4433
FEV1 % predicted	112.22	21.336
FEV1 LLN	1.935	.4935
FEV1-to-FVC ratio (%), predicted	83.09	10.57
FEV1-to-FVC ratio (%),predicted	113.02	29.41
FEV1-to-FVC ratio (%) LLN	75.55	1.353
Age in years	*47.26*	*19.076*

Table-2: Spirometry results and gender.

	Male	Female	P-value
FVC (L)	3.29±53	2.94±.5716	0.002
FEV1 (L)	2.93±656	2.51±519	0.000
FEV1/FVC (%)	89.03±5.86	85.47±5.107	0.004

Age had no significant correlation to FVC (Pearson correlation coefficient 0.094, p= 0.136), FEV1 (Pearson correlation coefficient 0.085, p= 0.178), or with FEV1/FVC ratio (Pearson correlation coefficient 0.018, p= 0.776). However, there was statistically significant difference in spirometry results of males and females. (p value= 0.002 for FVC, 0.00 for FEV1 and 0.004 for FEV1/FVC). 37 (14.5%) had restrictive pathology, 6 (2.4%) had obstructive pathology and 212 (83.1%) had normal lung function tests. 35 (13.7%) had mild restrictive dysfunction and 2 (0.8%) had moderate restrictive lung dysfunction.

Fig-1: Correlation of age and FEV1 and FEV1/FVC

Correlations

		Age	FEV1
Age	Pearson correlation	1	.085
	Sig. (2-tailed)		.178
	N	255	255
FEV1	Pearson correlation	.085	1
	Sing. (2-tailed)	.178	
	N	255	255

Correlations

		Age	FEV1/FVC
Age	Pearson correlation	1	.018
	Sig. (2-tailed)		.776
	N	255	255
FEV1FVC1	Pearson correlation	.018	1
	Sig. (2-tailed)	.776	
	N	255	255

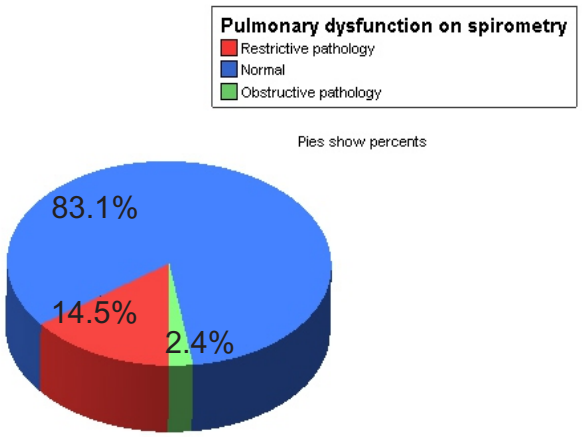

Fig-2: Restrictive pathology in study group

Discussion

Impaired lung function has attracted growing interest as a potential complication of diabetes.[10] Cross sectional studies have consistently shown that adults with diabetes have lower vital capacity than their non-diabetic counterparts[11] but such studies cannot establish the temporal sequence of events. Our study included 255 diabetic patients. 14.5% had restrictive pathology, 2.4% had obstructive pathology and 83.1% had normal lung function tests. 13.7% had mild restrictive dysfunction and 0.8% had moderate restrictive lung dysfunction. The results were similar to many previously published data. Atherosclerosis Risk in Communities (ARIC) Study, a biracial, community- based cohort of adults aged 45-64, was conducted to test the hypothesis that diabetes is associated with reduced lung function independently of known risk factors. In cross-sectional analyses, middle-aged adults with type 2 diabetes had significantly lower FVC, FEV1, FVC% predicted, and FEV1% predicted compared with their non-diabetic counterparts. These relationships were graded by fasting glucose, HbA1C, diabetes duration, and intensity of anti diabetic treatment and were independent of traditional risk factors. In prospective analyses, FVC declined faster in diabetic adults than in their non diabetic counterparts. Again, these associations were independent of known risk factors (i.e., age, smoking and central obesity) for lung function decline and showed graded associations with indicators of diabetes severity. In this study, the non diabetic group had an annual FVC decrease of 58 ml/ year. Our results are generally consistent with those of prior cross-sectional studies which also have demonstrated lower FVC and FEV1 in adults with prevalent diabetes compared with their non diabetic counterparts[12,13,] especially when diabetes was of longer duration and required insulin treatment and when diabetic individuals had existing complications of the disease.[14] Furthermore, in non diabetic adults, lower FVC and FEV1 were associated with higher fasting glucose and with hyper-insulinemia and estimated insulin resistance. Some previous studies offer prospective data on diabetes and subsequent lung function. Lange et al followed 17, 506 Danish adults in the Copenhagen City Heart Study for 15 years. At baseline, FVC and FEV1 were consistently lower in diabetic individuals, with a more than 8% difference in FVC between diabetes and non diabetes (similar to what we found in ARIC: 96 vs 103%). However, longitudinal analyses showed no influence of diabetes on subsequent declines. FVC declined 24 ml/year in diabetic women and 39 ml/year in diabetic men. Davis et al followed 125 Australian patients with type 2 diabetes for a mean of 7 years. FVC and FEV1 continued to decline at annual rates of 68 and 71 ml/year, respectively. Declines in FVC and FEV1 were more rapid in patients with higher baseline A1C. Nevertheless, no non diabetic control group was assembled for comparison. Litonjua et al[15] performed a nested case-control analysis in 352 men who developed diabetes and 352 non diabetic men in the Normative Aging Study. The study showed that although individuals with diabetes had lower FEV1 and FVC at all time points, they had only 5.4 ml/year greater declines compared with control subjects after diagnosis of diabetes. Like other case control studies, it was possible that only healthy subjects who were at risk for diabetes completed the lung function tests.

Although the underlying mechanism relating diabetes to reduced lung function remains unclear, previous studies suggest several possible explanations including glycosylation of chest wall and bronchial tree proteins, thickening of basal lamina,[16] and perhaps increased susceptibility to respiratory infections. Additionally, hyperglycemia, inflammation, and diabetes-related oxidative stress have been shown to induce muscle dysfunction.[17] The effects could be mediated by pro-inflammatory master regulator molecules which themselves might be subject to further inflammation by hyperglycemia.[18,19]

Other studies of lung function in pre diabetics complicate causal inferences. In particular, several recent prospective studies, including the ARIC Study, have demonstrated that reduced lung function is an independent predictor of incident type 2 diabetes.[20] In this study, the associations between diabetes status and lung function were more significant cross-sectionally than prospectively. These results suggested the notion that abnormalities in lung function precede diabetes and then continue after diabetes onset. Furthermore, it is possible that the findings in ARIC fit into the broadening picture of mild organ dysfunction associated with altered gene expression found in the common conditions underlying diabetes. Attention to the lung as a possible target organ of diabetes-related injury has been highlighted recently by the approval of delivery of insulin by inhalation.[21] A recent meta-analysis of randomized controlled trials of at least 12 weeks' duration[22] reported a greater decrease in FEV1 from baseline among those taking inhaled insulin than did those in the comparison group. Limitations of the

present study included a hospital-based population, cross-sectional study design, lack of data on potential confounders and small sample size that can potentially decrease precision of our estimates. Finally, given the strong relation between type 2 diabetes and central adiposity, lack of adjustment for BMI and waist circumference leaves concern about the possibility of confounding. Using a multivariate study analysis, taking into account the potential confounders by using logistic regression and using a case control study design comparing diabetics with non-diabetics would have improved the strength of our study. In summary, this study supports the notion that lower lung function, particularly decreased vital capacity, is common among diabetics. Additional research is required to identify pathophysiologic mechanisms and to determine clinical significance of this association. In the meantime, clinicians should pay heightened attention to pulmonary function in their patients with type 2 diabetes. To date, the clinical studies relating to pulmonary dysfunction in diabetic subjects have been cross-sectional in design. Although abnormalities of pulmonary function have been detected in some diabetic subjects, the following questions still need to be addressed: What is the temporal pattern of pulmonary involvement in diabetic subjects? What is the influence of duration of diabetes and glycémic control on the progression of pulmonary dysfunction? What is the relationship of abnormal pulmonary function to existing diabetic complications? What is the relationship of subclinical pulmonary dysfunction in terms of the development of pulmonary disease?

These important questions could be addressed by means of a carefully controlled longitudinal study.

While mild reduction of diffusing capacity causes few symptoms at rest, such an abnormality of lung function may impair exercise tolerance; future studies assessing the effect of exercise on the pulmonary function of diabetic subjects should be undertaken. Since abnormalities of pulmonary mechanics in IDDSs may be related to NEG-induced alterations of pulmonary connective tissue, the question as to whether NEG alters collagen/elastin mechanics needs to be addressed at a bio-mechanical level. In vitro studies assessing the effect of hyperglycemia on the mechanical properties of collagen and elastin in connective-tissue meshwork may be contributory to addressing the issue. Finally, the finding in certain studies that pulmonary function is abnormal in some diabetic subjects constitutes sufficient evidence to suggest that the lung should be considered a "target organ" in diabetes mellitus. However, the clinical relevance of these findings in terms of the development of respiratory disease has yet to be ascertained.

Conclusion

These data support the notion that the lung is a target organ for diabetic injury. Additional research is required to identify pathophysiologic mechanisms and to determine clinical significance.

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